PROTECTING ACCESS TO IMMUNE GLOBULINS FOR CANADIANS

FINAL REPORT OF THE EXPERT PANEL ON IMMUNE GLOBULIN PRODUCT SUPPLY AND RELATED IMPACTS IN CANADA

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CHAIRPERSON'S FOREWORD

On behalf of the Expert Panel on Immune Globulin (IG) Product Supply and Related Impacts in Canada (the Panel), it gives me great pleasure to report the Panel's findings. The issues which were the mandate of the Panel are of critical concern to Canadians, particularly patients and clinicians who depend on the provision of safe, accessible IG and other plasma derived products. It was an honour for all the members to serve on the Panel and to play a role in considering the critical issues in our mandate.

Two decades ago the Commission of Inquiry on the Blood System in Canada submitted its final report (known as the Krever Inquiry). The work of the Panel at this time offers the opportunity to review the scientific developments of twenty years and reflect on the changes which have occurred since the report of Justice Krever.

We could not have completed our work without the generous contributions of individuals representing patients and patient groups, health providers, policy makers, Canadian Blood Operators, manufacturers, plasma collectors, and other important stakeholders – both in Canada and across the world. On behalf of the Panel I would like to thank the many people who gave of their time to submit their thoughts and information, join in teleconferences or actually visit the Panel in person to enrich our discussion. I would also like to sincerely thank the Canadian Agency for Drugs and Technologies in Health and the library service at Health Canada for their extensive analysis of the literature to support our work.

The Panel would also like to highlight and appreciate the work of our 2 Canadian Blood Operators (CBS and Héma-Québec), the Provincial and Territorial Governments who fund their operations, and Health Canada, the national regulator – all of whom have worked hard over the last 20 years to rebuild confidence in the blood system and deliver high quality and safe blood services and products to Canadians.

Finally, I would like to thank my esteemed colleagues, the Deputy Chair, Dr. Francine Décary, and the two Special Advisors, Drs. Patrick Robert and Merlyn Sayers for their great work, and for enriching the discussion by contributing their years of experience and extensive knowledge. The Health Canada secretariat team that supported our work this past year was outstanding in their commitment and expertise and enabled the Panel to complete their work on behalf of Canadians. On behalf of the Panel I would like to sincerely thank them.

Penny Ballem, MD FRCP FCAHS
Chair, Expert Panel on Immune Globulin Product Supply and Related Impacts in Canada
March 29, 2018

EXECUTIVE SUMMARY

A safe and secure supply of blood and related products is a cornerstone of the health care system. Patients across Canada depend on having fresh and frozen blood components and other vital products manufactured from human plasma available to them on a daily basis for treatment of various conditions.

Over the years, the use of immune globulins (IG), the most widely used product derived from human plasma, has expanded from the treatment of patients who do not make antibodies to protect themselves from infection (immunodeficiencies) to patients across a broad spectrum of illnesses (hematologic, neurologic, rheumatologic, dermatologic) where it is used as an immune modifier. Given the high levels of IG use for increasing indications across modern medicine, and the large numbers of patients across the world who still do not have access to these medications, concerns have been raised about Canada's long term ability to ensure the ongoing supply of IG for Canadians.

In 2016/17 the combined volume of plasma collected by Canadian Blood Services (CBS) and Héma-Québec (H-Q) only accounted for 16.7% of the plasma required to meet the needs of Canadians for IG and other PDPs. The rest of the plasma for making these products used by Canadians is collected in the US from paid donors. This situation is not unique to Canada and the global dependency on one jurisdiction for meeting the global needs of IG patients has led to recommendations from various international advisory bodies as well as the fractionation industry to encourage jurisdictions to develop strategies to protect and enhance local plasma collection to support growing demand for PDPs.

In response to concerns raised about market conditions for IG and the long-term sustainability of Canada's IG supply, Health Canada established the Expert Panel on Immune Globulin Product Supply and Related Impacts in Canada (the Panel) in July 2017. The mandate of the Panel was to assess the long-term security and sustainability of Canada's immune globulin product supply, and to examine the potential impact on the Canadian blood supply should plasma collection be permitted to expand significantly in Canada.

Over a 8 month timeframe, from August 2017 to March 2018, the Panel engaged a wide range of experts and stakeholders including patient organizations and health provider groups in Canada, the 2 blood operators in Canada, a range of international experts in regulation and public policy related to the blood sector and blood system operations, and Canadian and international fractionation industry representatives. The Panel met 6 times and attended international conferences, undertook a broad based literature review, engaged provinces and territories (PTs), the National Advisory Committee on Blood and Blood Products, and federal officials responsible for oversight of regulation of the blood system and related products.

The Panel's task was not to make specific recommendations but to provide the information base which could inform decisions by PT governments and the government of Canada in regard to ensuring a sustained and secure supply of IG for Canadian patients and a resilient blood supply in Canada.

The Panel was very cognizant of the fact that 20 years ago, the Commission of Inquiry on the Blood System in Canada (the Krever Inquiry) tabled its final report. A significant focus of the Krever Inquiry related to the high rate of infection of Canadian hemophiliacs with human immunodeficiency virus (HIV) and hepatitis C (HCV) through their use of clotting factor concentrates which were plasma derived products. Much has changed in the 20 years since the Krever Inquiry findings were published. In the many discussions with stakeholders across Canada and internationally, the memory of this historical crisis in the safety of the Canadian blood supply and that of other countries around the world has not faded. In this context, the Panel spent a considerable effort to document the very significant changes which have occurred over the last 20 years in response to that tragedy.

Patients receiving IG can be divided into 2 major groups: those for whom the drug is life-saving and for which there is no effective alternative at this time and those whose illness can be positively impacted by the use of IG but for whom there are other therapeutic alternatives also available. There are a relatively small number of conditions and patient groups for which IG has been definitively shown to be effective and they account for the majority of use of IG.

Patients with Primary Immunodeficiency are completely dependent on IG for survival, with IG replacing antibodies which these patients cannot produce on their own. Patients with secondary immunodeficiency due to other illnesses such as chronic lymphocytic leukemia and multiple myeloma may also benefit from IG replacement therapy in some cases. Other conditions which are proven to respond to IG in some cases through its activity as a biologic modifier include: neurologic conditions (chronic inflammatory demyelinating polyneuropathy, myasthenia gravis, Guillain-Barre Syndrome, multifocal motor neuropathy) and immune thrombocytopenic purpura (ITP). There are multiple other situations where IG is used by clinicians, but many of these lack strong evidence of efficacy.

Demand for IG continues to increase steadily in Canada (6-10% per year) and globally. Canada is now the 2nd highest global user per capita of IG. In 2015/16 IG accounted for approximately ⅗ of the total spent on PDPs in Canada and the value of IG used for Canadian patients in 2015/16 was approximately US$286M. Across provincial jurisdictions in Canada, per capita consumption varies, but utilization has grown in every jurisdiction over the last 15 years. Québec has had the greatest per capita utilization of IG in the last 5 years, and Ontario the lowest.

Despite the growing demand for IG in Canada and internationally, there continues to be available global capacity in the plasma and fractionation sector and the Panel felt comfortable that there appears to be no emergency or crisis related to supply of IG for Canadians.

The Panel requested that the Canadian Agency for Drugs and Technology in Health (CADTH) examine whether there was anything on the horizon which would significantly alter the demand for IG –either a sudden reduction in demand due to a replacement product which was not derived from plasma or increased demand based on evidence that IG could positively impact a high prevalence health condition such as influenza or Alzheimer's disease. At this time there is no indication that the pattern of growth in demand for IG will dramatically change over the medium term.

The Panel felt it important to recognize that acute shortages can and have occurred in the supply of IG and PDPs over the past few decades. The variant Creutzfeldt–Jakob disease (vCJD) crisis in the UK caused an acute crisis in the supply of local plasma in the UK with resulting constraints on the supply of IG for UK patients for a significant period of time. However, a more common cause of an acute shortage is production shut-downs in individual fractionation facilities resulting in short term shortages of product from that supplier. Generally clients are able to access replacement products through other suppliers. The risks of acute shortages in the future are likely to stem from similar dynamics. There has been concern expressed in regard to the remote risk of a US Executive Order (for National Defense Resources Preparedness) or a collapse in a US/Canada trade agreement compromising supply of IG or other PDPs - the Panel concluded that this is very difficult to predict.

Strategies to risk manage acute and more prolonged shortages are essential to have in place in Canada. Over the last 15 years, both CBS and H-Q have put in place best practice strategic procurement processes to both protect against dependency on one supplier of IG and mitigate the risk of local production problems which could cause an acute shortage. Work does need to be done in Canada to develop a national prioritized list of patient groups dependent on IG and a process which will allow appropriate allocation of the product in the setting of a short term or more prolonged shortage.

Given the high usage of IG in Canada, a number of audits have been carried out in different provincial jurisdictions to understand patterns of utilization of this expensive product. These audits show that a significant proportion of IG use falls outside established criteria and guidelines. Other jurisdictions, particularly the UK, have achieved more success than Canada in optimizing the appropriate use of IG for patients for whom it is indicated, and as a result have a much lower per capita utilization rate. Overall, the Panel feels more needs to be done in Canada to enhance utilization management of IG. The Panel considers the UK IG demand management system to be a promising practice. It strengthened control / management of IG on an ongoing basis (everyday operations), and established priorities for patient access in case of a supply disruption (e.g. production issues that cause recalls and temporary shortages).

On the plasma supply side, there is growing international concern about the high global dependency on the US for the collection of source plasma which is the raw material used to manufacture IG and PDPs. Overall, the US supplies 74% of global source plasma for fractionation into IG and PDPs. The majority (>90%) of the global supply of source plasma is collected by the commercial sector from paid donors in plasma collection centres, with the majority located in the US. Capacity for commercial source plasma collection has been growing steadily in the US over the last 10 years (it increased by 168% between 2004 and 2015), both through increased capacity in existing commercial source plasma collection centres as well as a 55% increase in the number of new centres.

These expansions have been in step with the global growth in demand for IG. The Panel found no evidence to suggest that the source plasma market is reaching the saturation point. IG prices have remained very competitive during this time of significant growth in the demand for IG and PDPs, something attributed to growing competition in the fractionation industry and continued cost efficiencies in part related to economies of scale.

As noted earlier, Canada is currently only able to supply ~ 17% of the plasma needed to make IG and other PDP used by Canadians. A similar dynamic exists internationally for many countries. In response to this global dependence on US plasma collection, governments, blood operators and public policy organizations across the world are encouraging more domestic *self-sufficiency* in plasma collection, emphasizing the use of non-remunerated donors.

Québec in 2012 approved a plan by H-Q to start to address this by setting up sites in different geographic areas of the province where voluntary H-Q donors could donate source plasma. Since 2013/14, H-Q has established 4 Plasmavie centres and almost doubled the amount of plasma it sends for fractionation. H-Q now provides approximately 21% of the plasma needed for production of IG and other PDPs for patients in the province. CBS has also developed a business plan to increase source plasma collection from its donors.

Source plasma is also collected by the commercial sector in Canada – Prometic, a PDP manufacturer in Winnipeg, has operated a source plasma collection centre using paid donors for many years. Recently, Canadian Plasma Resources (CPR) applied for and was granted a license to collect source plasma in Saskatoon and subsequently in Moncton, New Brunswick. Both centres use paid donors. Both Prometic and CPR have plans for future expansion in Canada.

One of the important dynamics impacting the future of the global plasma supply is the strong public policy position for using volunteer unpaid donors for source plasma collection and a resistance to the use of paid donors. The rationale for this position includes concerns about safety of products made from paid donors, ethical concerns about the commodification of human plasma, and concerns that compensation for donating source plasma would diminish the commitment of volunteer donors of both whole blood and apheresis platelets.

In terms of safety, the global tragedy of the 1980s (as described in Canada by Krever) resulted in a significant international overhaul of legislation and regulation, systems and processes involved in screening and testing blood and plasma donors and their donations, the handling of plasma for fractionation, and the manufacturing processes involved in the production of PDPs. Current measures ensuring the safety of IG and PDPs are based on a multi-pronged approach. Many of the steps taken to assure the safety of these products are embedded in regulation and legislation and apply to all plasma

donors, volunteer or paid, as well as those agencies and facilities collecting and processing plasma to make PDPs. In addition to the regulatory framework, fractionation industry associations have rigorous quality programs (Quality Standards of Excellence, Assurance and Leadership (QSEAL)/International Quality Plasma Program (IQPP) standards in particular) which call for requirements beyond regulations which further enhance the safety of IG and other PDPs. The outcome of these changes has been dramatic: **there have been no confirmed cases of disease transmitted through PDPs in over 2 decades.**

The issue of paid source plasma donors was referenced frequently by patient groups and providers who spoke to the Panel. Their submissions reflect the international dynamics on this topic. Essentially patient groups are knowledgeable about the difficulties inherent in meeting collection targets and the high operating cost of collecting sufficient source plasma using exclusively volunteer unpaid donors. For patients and their representative organizations, given the remarkable safety record of IG and PDPs over the last 20 years, the major concern is not the issue of using paid donors but relates to assuring an adequate supply of plasma for patient needs which they view as the paramount safety risk. Their position is that both paid and unpaid donors are necessary to ensure an adequate supply of IG and other PDPs for patients.

The Panel spent considerable time and effort examining volunteer and paid donor plasma collection operations – the data are interesting and reflect the significant changes which have occurred in the plasma and PDP sector over the last 20 years. Across Europe, Australia and North America, the only jurisdictions that have achieved 100% self- sufficiency for plasma collection are those that have permitted paid plasma donors. Jurisdictions that permit payment of source plasma donors have a significantly higher plasma collection capacity on a per capita basis compared to those jurisdictions where compensating source plasma donors is prohibited. In addition, the cost of collecting large volumes of source plasma utilizing volunteer donors is 2-4 times more expensive than the commercial plasma collection model and thus it remains more economical for jurisdictions to purchase IG and PDPs from the commercial market, all of which are made from plasma from paid donors. Finally evidence indicates that notwithstanding the funding for blood operators to meet collection targets to achieve self-sufficiency, often source plasma programs based on volunteer donors just simply can't make their targets.

Other evidence revealed the evolving nature of a voluntary donor – data from the European Union reveal that in Europe, incentives for voluntary donors are diverse and in many instances have a value equivalent or even greater to what would be considered payment in Canada and other jurisdictions – thus the definition of a volunteer donor is shifting. Furthermore, there is increasing discussion amongst longstanding non-profit blood operators that greater

The Panel recognizes that "voluntary/volunteer" and "paid" are imperfect terms to differentiate donors and the donation event, but they are used in this report to distinguish between unpaid/uncompensated/nonremunerated and paid/compensated/remunerated donors/donations. There is no suggestion that *any* donations are "involuntary" in the sense of being mandatory or forced.

incentives are going to be needed to sustain engagement and commitment of volunteer blood and source plasma donors – the recent plans announced by Sanquin the national transfusion service of the Netherlands is a good example of this trend.

The question of whether Canada should increase its self-sufficiency in plasma collection and to what degree was a major focus of the Panel. The Panel had a strong consensus that Canada needs to make a much more significant contribution to the collection of source plasma – the Plasmavie program and the desire of CBS to increase collection of source plasma from their donors are an appropriate response to the significant dependency on the US as a source of plasma. On the issue of what level of self-sufficiency should be targeted, it is appropriate for Canada *at a minimum* to be able to provide sufficient plasma to meet the needs of the one group who are truly life dependent on IG – those patients with primary immunodeficiency (PID). This would ensure that these patients are protected in the unlikely event of a severe shortage. Volume targets beyond this minimal expectation should reference priority clinical needs.

Importantly, the move to collect more source plasma by CBS and H-Q needs to be based on solid business principles and learnings and/or partnerships with the private sector who have significant expertise. Increased source plasma collection by CBS and H-Q cannot be undertaken at *any* cost. There is a significant premium related to the cost of collecting high volumes of plasma from volunteer source plasma donors (between 2-4 times more costly) – this is recognized by CBS and was reaffirmed by discussions with other jurisdictions. There is a growing acceptance across jurisdictions that self-sufficiency strategies should avoid being totally dependent on any one country for source plasma donors, and achieve a balance between dependency on the commercial market, and the incremental cost of collecting source plasma from local volunteer donors. The approach taken in Australia where the cost and feasibility issues of source plasma collection using volunteer unpaid donors are weighed against the benefits of a higher level of self-sufficiency – on a regular basis, plasma collection targets and related budgets are set by the National Blood Authority (NBA); the rest of the needs of Australians are met through competitive procurement of PDPs off the commercial market.

Given that there are a number of provinces in which commercial plasma operations are currently permitted, the Panel agreed that options could be carefully examined to ensure that all source plasma collected in Canada from Canadian donors (whether paid or volunteer) be made available for the needs of Canadian patients. There are a number of mechanisms whereby this could be achieved.

Finally the Panel recognizes that over the last 2 decades, CBOs have pursued multiple strategies to protect the supply of IG and PDPs for Canadian patients including strategic procurement, collection of local recovered and source plasma, supply guarantees, the use of toll fractionation and the concept of

regional self-sufficiency. These strategies should continue and be further enabled by enhanced source plasma collection by CBOs and the securing of all plasma collected in Canada to be returned for the use of Canadian patients.

One of the important issues the Panel was asked to review was the impact, if any, of expanded source plasma collections on the whole blood supply. The Panel examined the issue from a number of perspectives and acknowledges that there has not been a lot of research undertaken on this issue. The concern is in part confounded by the overall lower demand for red cells over the last 10 years, which was very pronounced in the US, but which is clearly attributable to changes in transfusion practice and reduced demand for blood. There is no compelling data to suggest that expansion of source plasma collection – whether with paid or unpaid donors - has negatively impacted the whole blood supply. However, we would caution that this is an issue which should be further researched and it requires ongoing oversight and vigilance. One particular issue worth monitoring is whether source plasma operations could affect recruitment of future volunteer apheresis platelet donors.

In the Panel's review of the full scope of the IG and related plasma sector, information was collected to provide a more robust understanding of the regulatory systems in place to protect the public in both Canada and other jurisdictions. Generally the Panel concluded that the sustained safety of IG and PDPs over the last 20 years reflected effective regulation and oversight of the blood, plasma and PDP sectors. There were a number of areas where the Panel felt enhancements could be considered to further strengthen oversight and align with evolving international best practice. Canada would benefit from a more structured and coherent approach to surveillance and early warning in regard to threats to the blood supply. Currently, much of the surveillance activity depends on various data sets and the voluntary sharing of data by PTs resulting in time lags in reporting and a lack of consistency and comprehensiveness. Ideally there should be one committee which has the exclusive mandate to acquire comprehensive data on a regular and timely basis and provide the appropriate, regular analysis and advice to Health Canada or PTs in regard to evolving threats. Health Canada could also consider incorporating into the blood regulations some of the voluntary standards developed by the PDP sector including the requirement to report source plasma donor data – both in regard to seroprevalence rates and donor safety issues for source plasma donors given their frequent donations.

While the focus of this report is assuring continued access to IG for Canadians, we also heard from patient groups who expressed concerns about how the current system limits access to other PDPs they need. The Panel is concerned about these issues and suggests a first step would be ensuring a review of any new PDPs being considered for Canada be done by CADTH to ensure clarity in regard to their effectiveness and the appropriate indications. There was significant concern by patient groups and some clinicians that there would be a move to place PDPs on provincial drug plans which would increase the cost for many patients due to co-pays (an issue which the Panel felt was outside their mandate). However the Panel noted that in Canada, the longstanding principle that plasma-derived products be provided to patients at no cost along with all other blood and component products, is something which should be reaffirmed or at least revisited by the PTs and the federal government together. Given donors across the country contribute their plasma for these products now, and potentially will do so to a

greater degree in the future, clarification of this longstanding principle and the development of a transparent approach across the country to this equity of access issue would be helpful.

In summary, much has changed since the release of the Krever Commission report in 1997. PDPs are safe, the plasma sector has been able to respond and react to continuing changes in demand over the last 20 years ensuring care for patients in Canada. New products continue to be developed to address serious health conditions. Our CBOs use sophisticated strategies with the support of provincial, territorial and federal governments to ensure the sustained supply of safe and affordable products for patients in Canada. However, like most of the world, we are too dependent on one jurisdiction (US) for the supply of the vital raw material used to make these products. Canada needs to do more to collect plasma and take other steps to enhance our self-sufficiency in meeting the needs of our citizens for PDPs. As discussed there are a number of decisions to be made and strategies to be considered. In the implementation of the strategies, there needs to be transparency for the public and stakeholders, adherence to good business principles with flexibility in the approach where appropriate, due consideration of the taxpayer, and ongoing attention to the outcomes with the capacity to adjust where necessary. The Panel has consolidated much of the evidence available related to these issues in this report and we respectfully submit it to the Deputy Minister of Health Canada in the hopes that it will enable a robust discussion across the country on the way forward in a critical area of public health care in Canada.

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LIST OF ABBREVIATIONS

A-PLUS	American Plasma Users Coalition
BCA	Blood Centers of America
BSE	Bovine spongiform encephalopathy
CADTH	Canadian Agency for Drugs and Technologies in Health
CBOs	Canadian Blood Operators (CBS and H-Q)
CBS	Canadian Blood Services
CIDP	Chronic Inflammatory Demyelinating Polyneuropathy
CJD	Creutzfeldt-Jakob disease
CPR	Canadian Plasma Resources
CRC	Canadian Red Cross
CSA	Canadian Standards Association (CSA Group)
CUPE	Canadian Union of Public Employees
EBA	European Blood Alliance
EU	European Union
FDA	Food and Drug Administration (US)
FPT	Federal, Provincial, Territorial
HAE	Hereditary Angioedema
HAV	Hepatitis A Virus
HBV	Hepatitis B Virus
HEV	Hepatitis E Virus
HCV	Hepatitis C
HIV	Human Immunodeficiency Virus
H-Q	Héma-Québec
IG	Immune Globulin
INESSS	Institut national d'excellence en santé et en services sociaux (QC)
IPFA	International Plasma Fractionation Association
ISBT	International Society of Blood Transfusion
ITP	Idiopathic Thrombocytopenic Purpura
IVIG	Intravenous Immune Globulin
MG	Myasthenia gravis
MRB	Marketing Research Bureau

NBA	National Blood Authority (Australia)
NAC	National Advisory Committee (on Blood and Blood Products) (sub-committee of PTBLC)
NAT	Nucleic Acid Test
PDP	Plasma Derived Products
PHAC	Public Health Agency of Canada
PID	Primary Immune Deficiency
PLUS	Platform of Plasma Protein Users (PLUS)
PPTA	Plasma Protein Therapeutics Association
PT	Provinces and Territories
PTBLC	Provincial Territorial Blood Liaison Committee
QSEAL	Quality Standards of Excellence, Assurance and Leadership
SCIG	Subcutaneous Immune Globulin
SID	Secondary Immunodeficiency
SP	Source plasma
TBV	total blood volume
TESS	Transfusion Error Surveillance Systems
UM	Utilization Management
vCJD	variant Creutzfeldt–Jakob disease
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

A safe and secure supply of blood and related products is a cornerstone of the health care system. Patients across Canada depend on having fresh and frozen blood components and other vital products manufactured from human plasma available to them on a daily basis for treatment of various conditions.

This report relates to ensuring safe and secure access to the medications which are manufactured from human plasma ("plasma-derived products" or PDPs) with a priority focus on immune globulin (IG). It speaks to the different roles of the various players involved in ensuring safe and secure access to PDPs. These players include:

- Patients across Canada who receive PDPs for their health conditions;
- Physicians who prescribe PDPs for their patients;
- Hospitals and health authorities across Canada that dispense blood products;
- Donors of blood and/or plasma on whom the manufacturers of PDPs depend;
- Canadian blood operators (CBOs), i.e. Héma-Québec (H-Q) and Canadian Blood Services (CBS) that collect and distribute blood and plasma and purchase PDPs for patients across Canada;
- Commercial fractionators that manufacture PDPs across the globe;
- Health Canada which has the responsibility for regulating the blood and plasma collection centres and operations, fractionation plants and the licensing of PDPs for use in Canada;
- Provincial and territorial (PT) governments that fund the blood operators and are responsible for delivering health care to their residents.

Plasma is a yellowish coloured liquid component of blood that normally holds the blood cells in whole blood in suspension. It makes up about 55% of the body's total blood volume (TBV). It is the raw material manufactured into a range of medications used by Canadians both inside and outside the hospital setting.

1.1 ESTABLISHING THE HEALTH CANADA EXPERT PANEL

The growing use and need for IG and other PDPs for Canadian patients over the last 10-15 years have highlighted concerns in regard to protecting a safe and secure supply of these vital products. Furthermore, the growing global dependence on plasma collected in the US for the production of PDPs has led to recommendations from various global advisory bodies and associations which encourage jurisdictions to develop strategies to protect and enhance local plasma collection to support growing demand for PDPs. IG is the focus of concern, a sufficient supply of other PDPs not being an issue at this time.

In early 2017, CBS presented a business plan to federal, provincial and territorial (FPT) governments to increase its self-sufficiency through collection of source plasma from its voluntary donors. At the same time, the licensing by Health Canada of 2 new private plasma collection centres in Saskatchewan and New Brunswick raised concerns that commercial plasma collection centres that compensate their donors would have a negative impact on the recruitment and retention of CBS voluntary whole blood and source plasma donors.

In this context, the federal government struck the Expert Panel to examine the concerns raised and report to the federal Deputy Minister of Health, who would share the findings with his provincial-territorial counterparts as those responsible for most decision-making related to the blood system in Canada.

The Panel mandate was not to make recommendations but to:

- assess the long-term security and sustainability of Canada's IG product supply;
- look at the potential impact on the Canadian blood supply should plasma collection be permitted to expand significantly in Canada;
- examine emerging international practices and lessons learned that are relevant to the Canadian context.

The Terms of Reference that guided the Panel's work are attached as Appendix A. Biographies of the Panel members and special advisors are attached as Appendix B.

1.2 BACKGROUND TO THE ISSUE

Plasma is the raw material manufactured into a range of medications used by Canadians both inside and outside the hospital setting. Plasma comes from 1 of 2 sources:

- Recovered plasma – which is recovered from whole blood donations;
- Source plasma – which is collected directly from the donor by the use of a plasmapheresis (apheresis) machine. Collecting source plasma allows up to 3 times more plasma to be collected in 1 sitting, and a much greater frequency of donation.

The main plasma-derived products (PDPs) include:

- IG – used to treat patients who have a lack of normal immunity to fight infections (patients with primary and secondary immunodeficiency) and other patients with conditions for which IGs appear to have a beneficial effect through modification of the immune system. IG comes in various forms for administration – intravenous immune globulin (IVIG), subcutaneous immune globulin (SCIG), and intramuscular immune globulin (IMIG). In this report, they will be collectively referred to as IG unless otherwise noted;
- Clotting factors (like Factors VIII and IX) – to treat individuals with hemophilia and other clotting disorders;
- Albumin – to maintain fluid volumes and circulate proteins through the body;
- Other protein replacement therapies for rare congenital deficiencies such as:
  - Alpha-1 antitrypsin
  - Antithrombin III
  - C-1 Esterase inhibitor[1]

IG is the most heavily used PDP in Canada and globally. This shift happened with the development of recombinant (not derived from plasma) clotting factors (late 1980s and 1990s) for the treatment of the majority of hemophilia patients. Over the years, the use of IG has expanded from the treatment of patients who do not make antibodies to protect themselves from infection (immunodeficiencies) to patients across a broad spectrum of illnesses (hematologic, neurologic, rheumatologic, dermatologic) where it is used as an immune modifier.

Given the increasing indications for IG across modern medicine, and the large numbers of patients across the world who still do not have access to these medications, concerns have been raised about Canada's long term ability to ensure the ongoing supply of IG for Canadians.

Thousands of Canadians depend on PDPs on a regular basis, whether as an essential drug that keeps them alive, or one that significantly improves their quality of life. The main conditions treated by IG and other PDPs are described in Chapter 2.

An average patient with primary immune deficiency (PID) in Canada receives between 30g and 40g of IG a month. Between 9 and 12 donations per month are required for 1 patient. (Canadian Immunodeficiencies Patient Organization submission)

Treatment with IG and other PDPs often occurs in hospital, or, in some cases, in the community. PDPs are supplied to Canadian hospitals by CBS and H-Q which issue these products to patients through the

hospital blood banks. In this report, CBS and H-Q will be jointly referred to as Canadian blood operators (CBOs) when they play the same role in their respective regions.

PDPs are manufactured using the process of fractionation in specialty facilities around the world. Both CBOs send plasma collected from their voluntary donors to their contracted fractionators for production of IG and other PDPs (see Section 4.1.1). The majority of IG and other PDPs used by Canadian patients are imported by CBOs from these contracted fractionators, and are derived from US paid donors.

In 2016/17, the recovered and source plasma collected by H-Q from voluntary donors constituted 21% of the plasma needed to make the IG required for the province of Québec, while CBS collected only 15.8% of the plasma needed to make the IG required for the rest of the country. Combined, the CBOs collected 16.7% of the plasma required – henceforth, rounded up to 17%. The rest of the plasma used for making IG and PDPs used by Canadians is collected in the US from paid donors. This dependency by Canada on US plasma collection to meet the need of Canadian patients is a concern which the Panel was asked to address.

In the late 1990s, CBS and H-Q (serving the needs of Québec) were created to replace the former Canadian Red Cross (CRC) Blood Transfusion Service. The CBOs are non-profit organizations funded by PT governments to recruit voluntary donors, operate whole blood collection, whole blood processing, and their related blood product distribution systems for Canada. CBOs also procure and distribute a formulary of PDPs that have been approved and funded for distribution by the PT governments.

1.3 KREVER INQUIRY

Twenty years ago, the Commission of Inquiry on the Blood System in Canada (the Krever Inquiry) tabled its final report. Based on the Krever Inquiry recommendations, the Canadian blood system underwent a major overhaul with the establishment of 2 new organizations with the responsibility for blood operations across Canada - H-Q (Québec only), and CBS (for the rest of the provinces and territories (PTs)).

A significant focus of the Krever Inquiry related to the high rate of infection of Canadian hemophiliacs with human immunodeficiency virus (HIV) and hepatitis C (HCV) through their use of clotting factor concentrates which are PDPs. The final 1997 report recommended that the Canadian blood supply system be governed by 5 basic principles:

a) "Blood is a public resource.
b) Donors of blood and plasma should not be paid for their donations, except in rare circumstances.
c) Whole blood, plasma, and platelets must be collected in sufficient quantities in Canada to meet domestic needs for blood components and blood products.
d) Canadians should have free and universal access to blood components and blood products.
e) Safety of the blood supply system is paramount."[2]

Much has changed in the 20 years since the Krever Inquiry findings were published and in pursuing its mandate, the Panel revisited a number of these topics, including payment of donors, plasma sufficiency, and safety of PDPs.

1.4 WORK OF THE PANEL

The Panel's work, supported by a staff secretariat provided by Health Canada, included the following:

- A review of the published scientific literature;
- A review of relevant grey literature originating from a wide range of sources;
- Review of key documents made available through the FPT governments in Canada;
- A review of key position papers by international bodies concerned with blood systems and PDPs;
- Attendance at the 2017 *IPFA/BCA 3rd Global Symposium on the Future for Blood and Plasma Donation*, co-hosted by the International Plasma Fractionation Association (IPFA) and Blood Centers of America;
- Review of phase III and IV clinical trials of potential IG replacement products (using www.clinicaltrials.gov, the Cochrane libraries, www.Clinicaltrialsregister.eu);
- Review of input from both CBOs in Canada;
- Input from stakeholders including through written submissions, telephone roundtables, and in person meetings and interviews;
- Interviews with technical experts and leaders in blood and plasma systems internationally;
- Discussions with staff from governments across Canada (see Appendix C).

The chapters that follow provide:

- A summary of the evidence available relevant to demand issues, with a focus on IG; (Chapter 2: Demand for IG (and other PDPs) and Plasma);
- A summary of the evidence available relevant to the supply of PDPs, with a focus on IG; (Chapter 3: Supply of Plasma, IG and Other Plasma-Derived Products and Related Regulations);
- An overview of questions related to product safety and security of supply, including concepts of self-sufficiency (Chapter 4: Secure and Sustainable Supply of PDPs and Blood for Canadians);
- An overview of the range of interests and perspectives held by the stakeholders engaged by the Panel (Chapter 5: Key Stakeholder Perspectives);
- The Panel's interpretation of and perspective on the evidence found and stakeholder views heard. (Chapter 6: Conclusion).

CHAPTER 2

DEMAND FOR IG (AND OTHER PDPS) AND PLASMA

In assessing the short, medium and long-term (2, 5, 10+ years respectively) security and sustainability of Canada's IG supply, the Panel reviewed the current and future demand for IG and the impact of these trends on the demand for plasma, the source material for IG and other PDPs.

2.1 DEMAND FOR IG AND OTHER PDPS IN CANADA AND GLOBALLY

2.1.1 CANADIANS RELYING ON IG/PDPS

Patients receiving IG can be divided into 2 groups: those for whom the drug is life-saving and for which there is no effective alternative at this time and those whose illness can be positively impacted by the use of IG but for whom there are other therapeutic alternatives available (Table 2.1). This distinction is important in the setting of constrained supply or interruptions of supply.

The conditions listed in Table 2.1 capture the major groups of patients for whom IG provides clinical benefit based on robust evidence.

Table 2.1: Major Groups of Canadian Patients Relying on IG

Life-saving	
1	Primary Immunodeficiency (PID)
Disease-Altering with Alternative Treatment Available	
1	Secondary Immunodeficiency (SID)
2	Idiopathic Thrombocytopenic Purpura (ITP)
3	Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
4	Myasthenia Gravis (MG)
5	Guillain-Barré Syndrome (GBS)
6	Multifocal Motor Neuropathy (MMN)

Over the years, IG has been examined as a potential disease-modifying treatment for many other common conditions including established Alzheimer's disease, sepsis, septic shock, influenza, epilepsy,

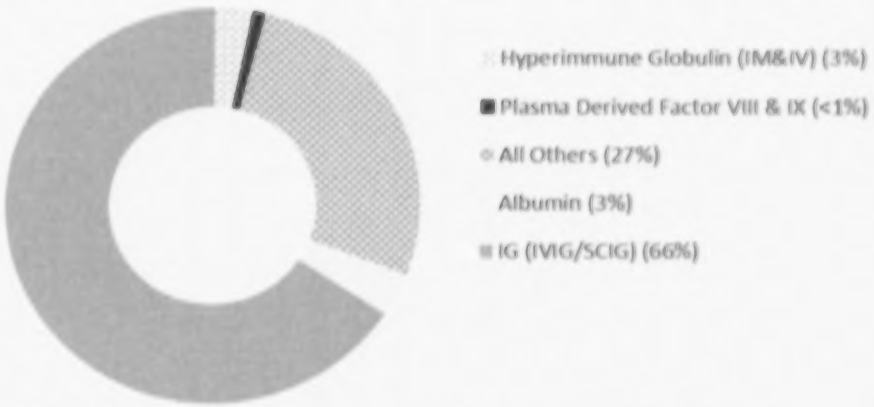
and during bone marrow transplantation. However, a rapid response review by the Canadian Agency for Drugs and Technologies in Health (CADTH) of the use of IG in these conditions reveals a lack of evidence to support the use of IG in these situations[3] (see Section 2.1.3 for additional information on CADTH's review). Based on case reports, there are many other patients who have been and continue to be treated with IG, however the evidence supporting IG as an effective intervention is lacking.

Other PDPs are also used to treat a number of other conditions such as von Willebrand Disease (vWD, treated by vWFactor), Alpha-1 Antitrypsin Deficiency (treated by Alpha-1 Antitrypsin replacement therapy) and hereditary angioedema (HAE, treated by C1 esterase inhibitor).

2.1.2 DEMAND TRENDS: PAST AND CURRENT

IG is the lead product among PDPs used in clinical care in Canada and much of the developed world. This is the result of the shift in the 1990s from plasma-derived clotting factors to recombinant proteins for the care of hemophiliacs. In Canada, IG accounts for approximately ⅔ of the total spent on PDPs in 2015/16 (Figure 2.1). Globally, in 2014, IG accounted for almost half (46%)[4] of the total spent on PDPs for patients. As a result of the dominance of IG among PDPs, the PDP sector is largely focused on responding to the demand for IG.

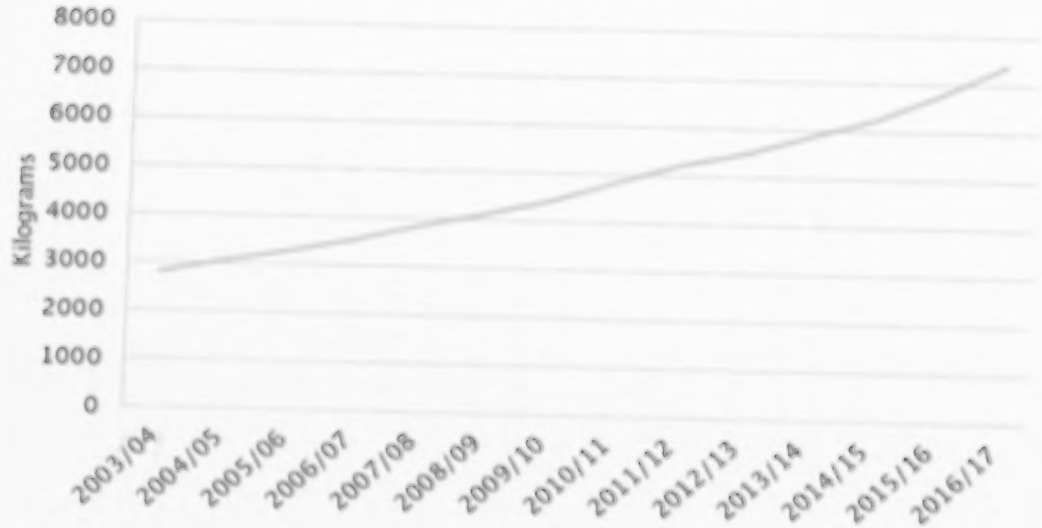
Figure 2.1: The Canadian PDP Market by Product (2015/16)
Total Market Value: US$433.9 million



Data from MRB, The Plasma Proteins Market in Canada 2015/16.

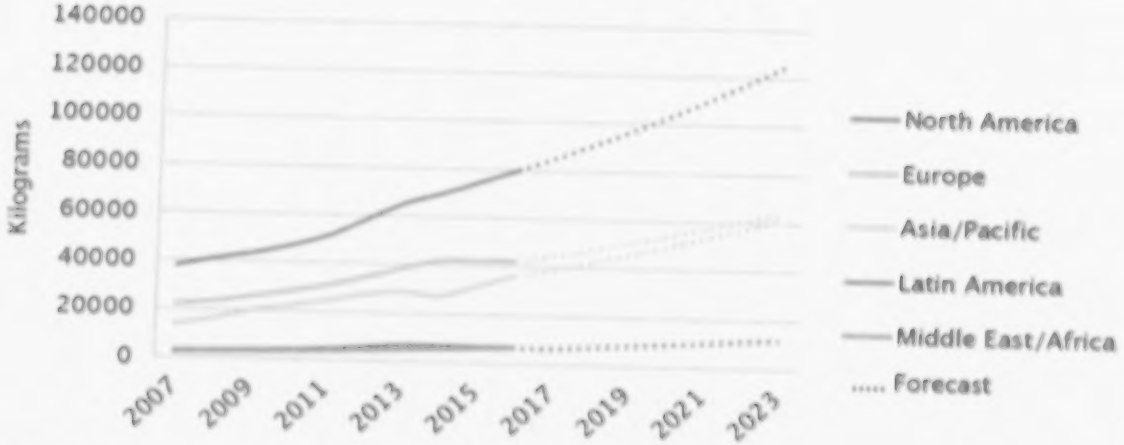
The historical trends in demand show that the demand for IG in Canada has been increasing steadily over the last 1.5 decades (Figure 2.2). Globally, the same pattern is observed (with the exception of the regions of Latin America, Africa and the Middle East) (Figure 2.3).

Figure 2.2: IG Demand in Canada – Actual



Data from CBS (2017); H-Q (2017).

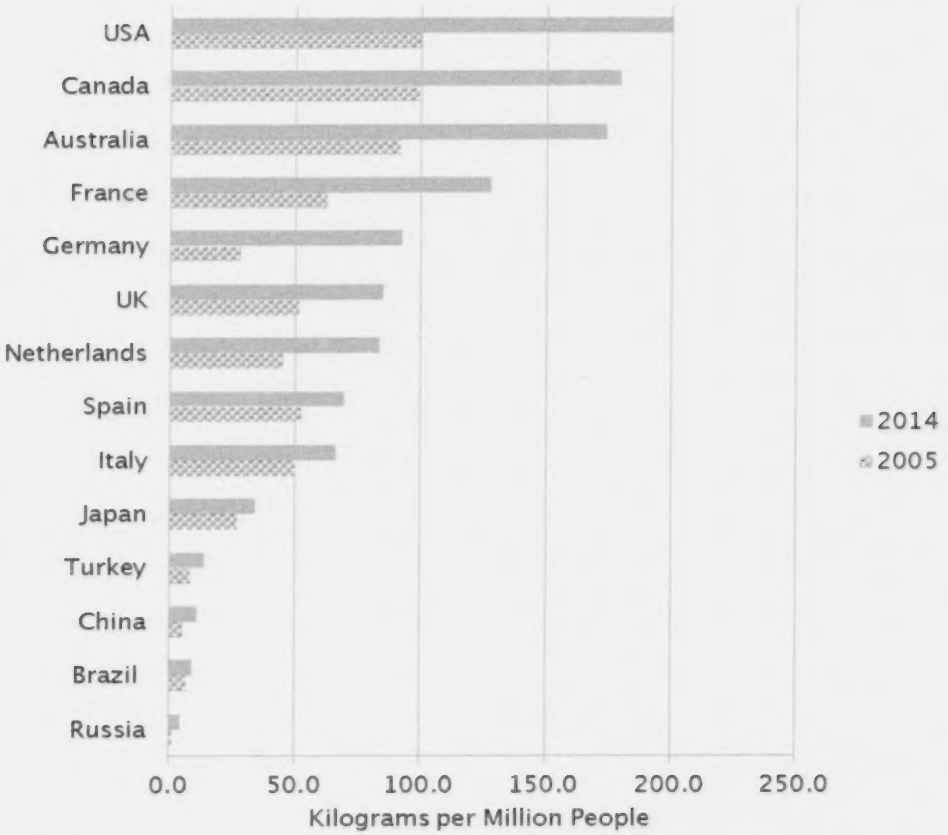
Figure 2.3: Global IG Demand – Actual and Projected



Data from MRB (2015) Forecast of the Global Immunoglobulin Market (2014–2023).

Canada has been a high user of IG for many years and Canada's per capita demand has been continuing to grow at a high rate. Canada is the second highest per capita user of IG in the world (Figure 2.4).

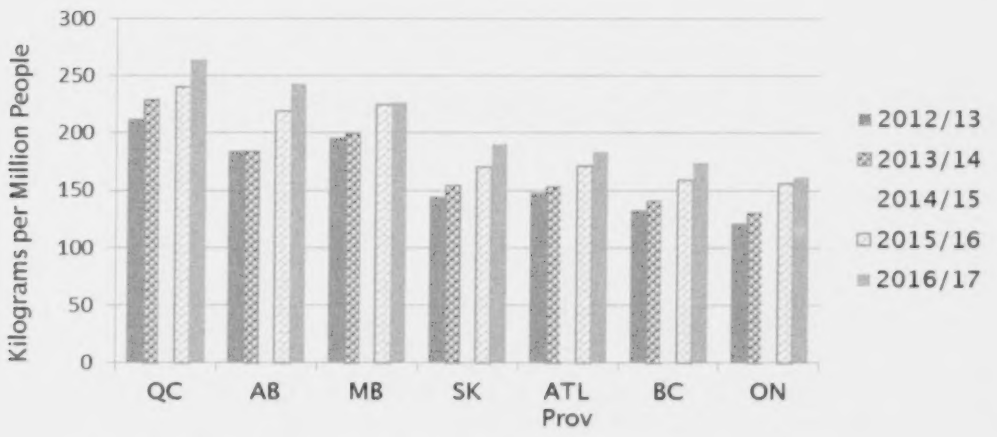
Figure 2.4: Global per Capita Utilization of IG



Data from MRB; PPFA/BCA 3rd Global Symposium, Sept 2017, Atlanta, GA

Across provincial jurisdictions in Canada, utilization has grown in every jurisdiction, and overall per capita consumption varies as noted in Figure 2.5. Québec has had the greatest per capita utilization of IG in the last 5 years, and Ontario the lowest.

Figure 2.5: Per Capita Consumption of IG in Canada



Data from CBS, 2017; H-Q, 2017, Statistics Canada

Different patient groups contribute to the overall demand metrics for IG. In examining the available evidence from Canada (Québec[5], Ontario[6]) and other international jurisdictions (Australia[6], UK[7], US[6]) over the last few years, the top 2 diagnoses for IG use are CIDP (a neurological disease) and PID.

The third-ranked diagnosis in terms of use across jurisdictions is frequently ITP or secondary immunodeficiency (SID). What is striking is that in the UK, which has a significantly lower per capita utilization rate, 7 health conditions for which IG is most frequently used account for 98% of utilization. For Australia, the third country behind Canada and the US in per capita use of IG, these conditions account for 83% of use. However, in the US and Canada (Ontario and Québec) which are #1 and #2 for per capita use of IG in the world, these conditions only account for 57% (US), 73% (Ontario), and 46% (Québec) of IG use, suggesting the need for more scrutiny over use of IG. Another evolving issue which has been mentioned as contributing to the growing use of IG is the growing incidence of obesity across patient groups: IG dosing is weight based and a specific adjustment is required for patients who are obese – if this is not done (using a dose calculator), then more product is prescribed than is necessary for the patient.

2.1.3 FUTURE DEMANDS DRIVEN BY CLINICAL RESEARCH

A review of clinical trial databases was undertaken by CADTH at the request of the Panel to assess whether there was any evidence in the research literature for a new high incidence indication for IG or for the development of a non-PDP that could replace IG. Either of these scenarios could significantly impact the IG supply in the short, medium, and long terms.

In terms of new indications for IG, the most significant risk in the last 15 years was the possibility that IG could be effective in the treatment of established Alzheimer's disease, a chronic illness with a high global incidence. Extensive studies demonstrate that IG is not effective in altering the course of this illness. Similarly, research examining the use of IG to treat other relatively high incidence disorders (e.g., influenza, epilepsy, or sepsis and related disorders) also showed no improvement in outcomes with the use of IG. The conclusion from the CADTH review was that at this time there appears to be no new indication on the horizon that would drive a significant increase in demand in the short to medium term[3].

In terms of new therapies that might replace IG, a search of phase III and IV trials to identify products that could enter the Canadian market within the next 5 years was conducted. Additional information was also received from stakeholders in this regard. The review did not identify any recombinant or other treatments for PID, multifocal motor neuropathy, or Guillain-Barré Syndrome. Trials underway for new treatments for the secondary immunodeficiency related to multiple myeloma and chronic lymphocytic leukemia were thought unlikely to change the demand for IG related to these conditions.

In ITP, there are existing recombinant platelet growth factor (non-PDP) treatments for chronic ITP which are licensed in Canada – with more in the research pipeline. Though 2 have been licensed in Canada for 5 years or more, they have only been added to a small number of PT formularies due to concerns with cost-effectiveness and side effects. Consistent with this, there has been a low level of prescribing of these drugs by Canadian clinicians.

Significant research investments continue to be made to develop IG replacement products, which may bear fruit over the longer term. Areas being explored include bovine-derived IG (using genetically-engineered animals) and recombinant proteins. For patients with PID or SID, which account for a significant amount of IG utilization, the challenge in developing a recombinant replacement is the need to develop a product which offers the comparable mix of antibodies found in human plasma.

For most other indications, where IG is used as an immune modifier, CADTH found little evidence of a replacement product in the medium term. H-Q reached the same conclusion in its 2016 review of potential IG replacements for treating autoimmune and inflammatory diseases and, in discussions with the Panel, CBS indicated its support for that conclusion.

While the Panel did not conduct a full review of clinical trials underway for PDPs other than IG, some patient groups track research trials on new products that may help treat their conditions. They report trials underway for new PDPs to treat Alpha-1 Antitrypsin Deficiency and HAE. For HAE, the new products could either increase demand for the PDP or replace its use with a non-PDP.

2.2 MANAGING THE USE OF IG

Differences in per capita use of IG across different jurisdictions could be explained by 1 or more of the following factors:

1. Different indications for use of IG;
2. Differences in the incidence of conditions in the population for which IG is indicated as a legitimate therapy;
3. Different clinical practice guidelines and/or dosing protocols for appropriate indications;
4. Use of IG which is not aligned with best practice guidelines.

All 4 factors were reviewed to assess which variables might account for the high use of IG in Canada. Generally, no evidence was identified to suggest that 1 and 2 are variables which could account for the high use of IG in Canada compared to other jurisdictions. However, 3 and 4 relate to how well the utilization of IG is managed and are discussed below.

Frequently, with an expensive product such as IG, jurisdictions implement a combination of clinical practice guidelines (CPGs) and utilization management (UM) processes. The Panel reviewed both CPGs and UM programs both in Canada and internationally to look at differences which might account for Canada's high per capita use of IG.

2.2.1 COMPARISON OF CLINICAL GUIDELINES

Canada does not have 1 "national clinical guideline" for the use of IG. The National Advisory Committee (NAC) supported the development of a series of IG guidelines published in 2007 and 2010[8] designed to help PT jurisdictions and their clinicians improve clinical practice in the use of IG. In Québec, general recommendations for IG use were issued by the Comité consultatif national de médecine transfusionnelle du Québec in 2005[9]. More recently (May 2017), the Institut national d'excellence en santé et en services sociaux (INESSS) published an evidence-based guideline for IG use in neurology, with further publications for other indications to follow[10].

CPGs for 4 conditions, issued by the NAC, select provinces (British Columbia[11], Saskatchewan[12], Manitoba[13], Ontario[14], the Atlantic Provinces[15]), and international jurisdictions (Australia[16], the UK[17] and the US[18-20] where available) were compared. The 4 conditions reviewed were PID, CIDP, acute ITP, and MG, which represent common indications for use of IG across 3 clinical disciplines (immunology, neurology and hematology). Generally, the CPGs for IG use in the 4 conditions were similar across jurisdictions however there were a few specific differences as noted below, which would certainly impact utilization:

PID: In Canada (with the exception of the Atlantic Provinces guidelines), initiation of IG treatment for PID did not require a firm diagnosis (as in the UK) or probable diagnosis combined with increased susceptibility to infection (as in Australia).

ITP: In Canada, the recommended dosage for the treatment of acute ITP in Canada was on the high end of the range and specifically double that of the UK. (Note: UK restricted the reimbursement of IG prescribed above the recommended minimal dose, unless clinically justified, after estimating that up to 60% of UK ITP patients were being over treated with IG)[7].

CIDP: In Canada, initiation of IG treatment for CIDP did not require a probable diagnosis (as in UK) or functional impairment (as in Australia).

MG: In Canada (and the UK), the dosage recommendations were higher than those in Australia for patients with MG; all jurisdictions examined required a specific level of severity to trigger IG use for MG.

2.2.2 IG UTILIZATION MANAGEMENT/MONITORING PROGRAMS – CANADA

In Canada, there are multiple players providing advice and oversight of IG use.

The National Advisory Committee on Blood and Blood Products (NAC) provides advice to CBS and the Provincial Territorial Blood Liaison Committee (PTBLC) (excludes Québec) on transfusion medicine practice and best practice utilization of all blood and blood products. Members of the NAC are transfusion medicine experts nominated by PTs and other experts nominated by CBS[21]. It is noted that while NAC members bring rich expertise in transfusion medicine, the membership of the committee does not reflect the multiple disciplines driving the expanded usage of IG (see Appendix C for list of members).

Provincial Territorial Governments – All provinces have either implemented an IG utilization program, have 1 under development, or are actively monitoring IG use. Utilization management programs are specific to each province but generally offer guidelines, dosage calculators and other decision support as well as requiring the clinician to complete an IG request form. However, both the NAC and other specialist clinicians who provide care to patients acknowledged that, in Canada, those physicians approving the release of IG (hematologists or hematopathologists responsible for the Blood Bank) find it very difficult to refuse the product to clinicians requesting it.

Audits of IG use have been performed in Ontario (2007, 2012, 2014)[22], and British Columbia (2001 and 2003)[23]. IG use has been detailed in Alberta (2001 and 2003)[23]. The use of IG has also been monitored on an annual basis most years in the 4 Atlantic provinces (2006/07-2016/17)[24]. Although those audit reports are not directly comparable (different definitions of inappropriate use, different time periods, and different utilization controls), they all suggest that a significant proportion of IG use falls outside established criteria, ranging from 10.5%[25] to 36.7%[23].

These results are consistent with feedback to the Panel from the members of the NAC and from stakeholder discussions with provider groups who felt that more could be done to better manage the use of IG across Canada.

2.2.3 IG UTILIZATION MANAGEMENT/MONITORING PROGRAMS – INTERNATIONAL

Internationally there have been significant efforts to create effective UM programs to manage the appropriate use of IG given the high rate of growth in utilization and its associated cost.

The UK is seen to have perhaps the most robust and successful national IG UM program[26], reflected in their low proportionate use per capita of IG (approximately half that of Australia or Canada (Figure 2.4)). Some speculate that UK clinicians and the health care system developed a culture of judicious use following the UK variant Creutzfeldt-Jakob disease (vCJD) crisis in which all domestic plasma collection stopped and the UK became entirely dependent on imports (see Section 4.1.2.2 for additional information on vCJD). The UK also has a national health service with more direct authority than the federated models in Australia and Canada. The UK UM system includes:

- clinical guidelines that prioritize conditions into 4 rank-order groups by need (high/medium/low priority and not approved);
- well-structured approval processes to assess requests differentiating between initial treatment and ongoing treatment;
- processes to limit reimbursement of hospitals and health care facilities for the cost of IG when not for approved uses[27].

In Europe, in 2014, a working group of experts and regulators from 36 European Union (EU) nations developed a consensus statement with 6 recommendations, which included a push for 'Ig demand management across Europe to ensure adequate supplies for all patients who need Ig treatment'[28]. Need was defined as those with life-threatening conditions who do not have alternate effective therapies. An additional goal of this process was to prioritize indications for use in the event of a shortage. (Temporary IG shortages had occurred in the late 1990s related to product recalls or regulatory compliance issues[29]). As examples of country-specific activities in the EU, Germany and France control unapproved use through restricting the reimbursement of products, with both jurisdictions providing expert review panels to assess exceptions to guidelines[27].

For the international jurisdictions discussed above, all but Australia have per capita use of IG well below that of Canada (Figure 2.4). In Australia, the National Blood Authority (NBA) indicated to the Panel that it is in the process of implementing a more robust UM system that draws from the UK experience, in

which clinicians need to specify how their patient meets the criteria or justifies an exception before the IG will be released. It is too early in its implementation to measure whether it is affecting utilization.

In discussions with experts in Canada related to UM of IG, the challenges faced by Blood Bank clinicians in Canada as the gate-keepers of managing utilization was repeatedly referenced by transfusion medicine stakeholders. IG and other PDPs are drugs, and all other drugs in health care institutions are managed through the pharmacy and overseen by the Pharmacy and Therapeutics Committees which set robust guidelines for use of pharmaceuticals in their institution. The possibility of moving PDPs under the oversight function of the hospital pharmacy committee to enable more effective management was discussed with the Canadian Society of Hospital Pharmacists. Interestingly, they shared with the Panel that pharmacists in Canada have no training related to PDPs, a fact that would make it challenging for pharmacists to take on this responsibility in the short term.

2.2.4 DEMAND AND ACCESS TO OTHER PDPS

While the focus of this report is assuring continued access to IG for Canadian patients for the medium and long-term, patient groups expressed concerns about how the current system limits needed access to other PDPs. Here, access refers to both the availability and affordability of PDPs for patients.

Once a prescription drug has been licensed by Health Canada for use in Canada, decisions about whether the drug is available either in the hospital or on a provincial drug plan (which usually involves co-payments by the patient) are made at both the FPT and hospital levels. For the public drug plans run by FPT governments, these decisions are based on systematic Common Drug Reviews conducted by CADTH. Those reviews systematically examine the clinical evidence and undertake pharmacoeconomic analysis, receive input from patients and have a verification step involving the manufacturers. A positive review by CADTH may not necessarily result in a listing decision; however, a negative review by CADTH usually results in the decision to not list the drug on a provincial drug plan[30]. Hospital-based decisions which relate to drugs available on the hospital formulary for in-patients are increasingly being made with the support of CADTH reviews.

Interestingly the process utilized by CBS for reviewing PDPs differs from this – CBS has a medical scientific advisory group that does an assessment of the clinical evidence while CADTH is asked to conduct a pharmacoeconomic analysis. The CADTH Drug Expert Committee is not involved in the medical/scientific review[31]. CBS makes recommendations to PT governments, and the secretariats responsible for blood services in PT governments collectively decide to add or not add PDPs to the list of funded products distributed through CBS.

In Québec, the INESSS, a health technology assessment agency advising the Minister of Health, undertakes a similar process to CADTH. The Québec government (Ministère québécois de la santé et des services sociaux) makes decisions on the purchase of PDPs based on recommendations by the Comité consultatif national en médecine transfusionnelle and assessments by INESSS[32]. H-Q is not involved at that stage, but once decisions are made it is responsible to procure and distribute approved products to hospitals.

Patient stakeholders referenced the longstanding principle in Canada that blood and PDPs be available free of charge to Canadians (reaffirmed in the Krever report). However, based on their input, it appears that even when listed by CBS, some PDPs are not available in some jurisdictions, and for those not listed, only a small number of provinces make the PDP available through other mechanisms which may require a patient co-payment. Alpha-1 antitrypsin, which is available in only 4 provinces, was cited as an example of this issue. A number of groups also pointed out that recombinant Factor VIII (no longer a PDP) continued to be funded as a blood product while other PDPs are treated differently.

CHAPTER 3

SUPPLY OF PLASMA, IG AND OTHER PLASMA-DERIVED PRODUCTS AND RELATED REGULATIONS

Manufacture of IG and other PDPs requires access to both plasma, as the raw material, and fractionation services. This chapter reviews the dynamics and the regulatory frameworks related to the supply and availability of plasma and the finished PDPs both in Canada and globally.

3.1 PLASMA SUPPLY

3.1.1 PLASMA COLLECTION IN CANADA - BY CBOs AND THE PRIVATE SECTOR

For decades, over 90% of Canadian plasma being sent for fractionation by CBOs has been recovered plasma. However, in 2012, a plan to collect more source plasma by H-Q has resulted in the establishment of 4 H-Q Plasmavie Centres where voluntary H-Q donors can donate source plasma. H-Q has since almost doubled the amount of plasma they send for fractionation, and now close to 50% of the plasma they send for fractionation is source plasma (Table 3.1). CBS has developed a business plan to increase source plasma collection from its donors. Despite this improvement in the supply of source plasma from Québec, as noted earlier in Chapter 1, Canada as a whole only supplies 17% of the plasma needed for the production of the IG used for the treatment of Canadian patients.

In 2010, as part of its strategy to provide more volunteer plasma for toll fractionation, CBS entered into a contract with Blood Centers of America (BCA) to purchase US recovered plasma from voluntary donors. This strategy also reduced costs for CBS with the combined cost of purchasing and processing plasma into PDPs less than buying commercial product[35]. The CBS recovered plasma figures in Table 3.1 include approximately 60,000 L/year[35] from BCA which amounted to a contribution of 6% of overall Canadian plasma needs (excluding Québec). Plasma sources cannot be mixed (US and Canadian) without prior Health Canada approval and the US recovered plasma is processed into separate products for CBS.

Table 3.1: Volume and type of plasma sent for fractionation by CBOs (in Litres)

	2013/14	2014/15	2015/16	2016/17
Canadian Blood Services[33]:				
Recovered Plasma (L)*	181,197 (97.7%)	176,018 (97.3%)	164,540 (96.3%)	168,305 (96.3%)
Source Plasma (L) (% of total Plasma sent for fractionation)	4,311 (2.3%)	4,877 (2.7%)	6,135 (3.6%)	6,395 (3.7%)
TOTAL Canadian plasma sent for fractionation by CBS (L)	185,508	180,895	170,675	174,700
% of Canadian (minus Québec) IG use met	--	--	17%	15%
Héma-Québec[34]:				
Recovered Plasma (L) (% of total plasma sent for fractionation)	51,508 (93.3%)	53,760 (87%)	50,653 (70.7%)	49,269 (51.4%)
Source Plasma (L) (% of total Plasma sent for fractionation)	3,692 (6.7%)	8,064 (13%)	21,031 (29.3%)	46,612 (48.6%)
TOTAL Canadian plasma sent for fractionation by H-Q (L)	55,201	61,824	71,684	95,881
% of Québec IG use met	14.5%	16.1%	17.7%	21%

CBO-collected Canadian plasma is manufactured into IG, Albumin, vWF and fibrinogen for use by Canadians. This contracted fractionation is performed by European and US private sector fractionators (Grifols, CLS Behring). Beyond this, Canada depends on continued access to commercial PDPs through negotiated contracts with global fractionators who manufacture the products from US paid plasma donors.

In addition to the collection of plasma by CBOs, plasma is also collected by the commercial sector in Canada.

Prometic Life Sciences Inc. collects plasma from paid donors in Winnipeg (this has been occurring for over 40 years) that is used for the manufacture of specialty hyperimmune globulins used in Canada and elsewhere (anti-D for the prevention of Rh disease of the newborn). Other hyperimmune globulins products are in development and Prometic will be manufacturing plasminogen in Canada (now under regulatory review).

The Panel recognizes that "voluntary/volunteer" and "paid" are imperfect terms to differentiate donors and the donation event, but they are used in this report to distinguish between unpaid/uncompensated/nonremunerated and paid/compensated/remunerated donors/donations. There is no suggestion that *any* donations are "involuntary" in the sense of being mandatory or forced.

Canadian Plasma Resources (CPR) was licensed recently to collect source plasma from paid donors in centres established in Saskatoon and Moncton. The plasma is sold to Biotest, a European fractionator.

Future plans for commercial plasma collection in Canada include the following:

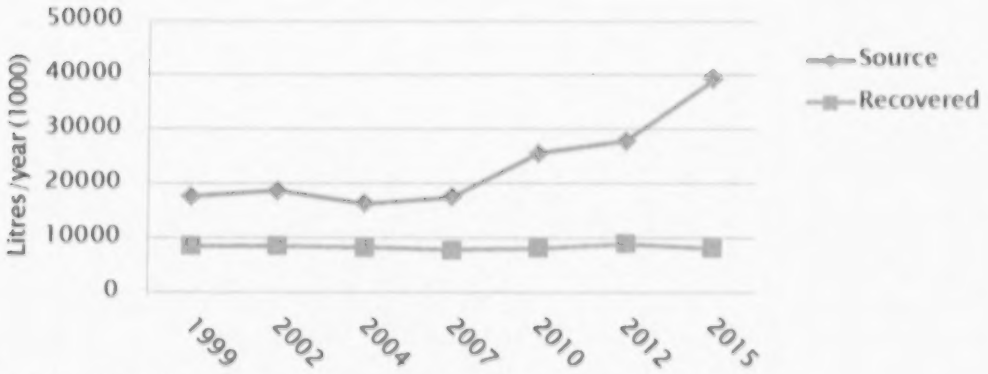
- CPR has plans to open a total of 10 source plasma collection centres in Canada, collecting 40,000 L/year per site at maturity. All centres are expected to have begun operation by the end of 2021. CPR expressed to the Panel its desire to work with the CBOs in making its collected plasma available to CBOs under contract; however, its initial offer to CBS had been declined[36].
- Prometic would like to open 6-8 commercial source plasma collection centres in Canada, each site producing 30,000 to 49,000K L/year at maturity, with the next centre planned to be opening in 2019 at the earliest[37].
- No other plans to open commercial plasma centres in Canada were identified.

3.1.2 INTERNATIONAL PLASMA SUPPLY

Trends in the overall global supply of plasma are well documented by the Marketing Research Bureau (MRB) and are discussed below.

Figure 3.1 illustrates the rise in plasma collected and fractionated globally over the past 15 years. The supply of recovered plasma has remained stable over this timeframe with the growth in plasma for fractionation coming exclusively from increased source plasma collection, with the majority coming from paid donors.

Figure 3.1: Global Plasma Fractionated

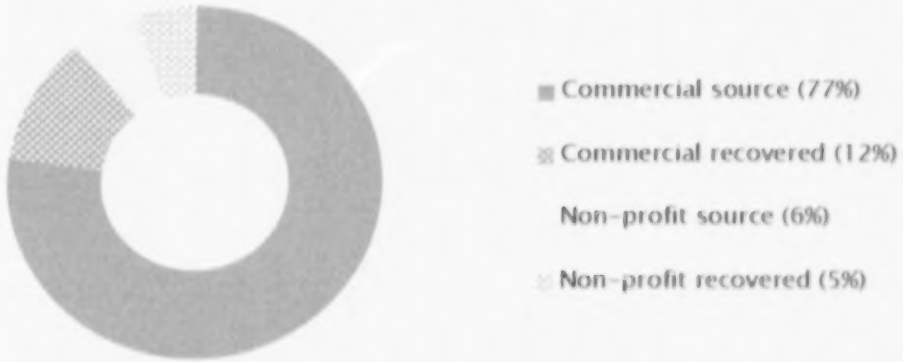


Data from: MRB (2017) International Directory of Plasma Fractionators

The flat/declining trend in the fractionation of recovered plasma collection is directly connected to the declining trends in whole blood collection due to reduced demand, which is related to more judicious

use of red blood cell transfusion over the last 10 years (see Section 4.4 re blood collection trends). In 2015, recovered plasma accounted for less than 20% of the overall global plasma supply used for fractionation of IG and other PDPs (Figure 3.2).

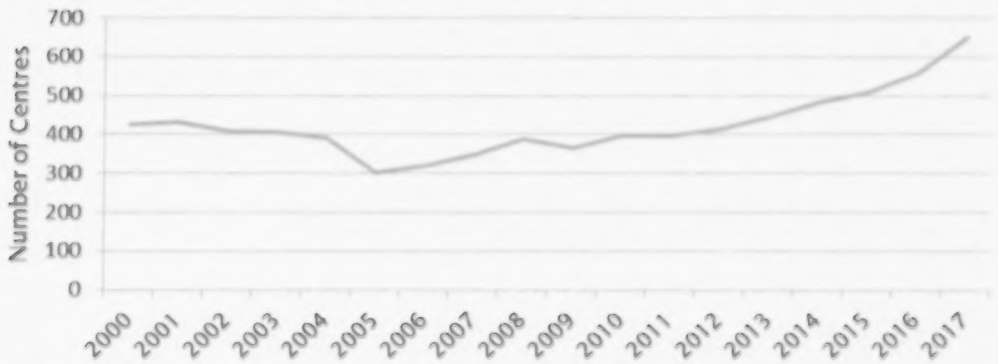
Figure 3.2: Global Type of Plasma Fractionated by Organizational Type (2015)



Data from MRB (2017) International Directory of Plasma Fractionators

The majority (>90%) of the global supply of source plasma is collected by the commercial sector from paid donors (Figure 3.2) in plasma collection centres, with the majority located in the US. Capacity for commercial source plasma collection has been growing steadily in the US over the last 10 years (168% from 2004 to 2015), both through increased capacity in existing commercial source plasma collection centres as well as the establishment of new centres (55% increase in new centres) (Figure 3.3).

Figure 3.3: Number of Plasma Collection Centres in the US



Data from Robert (2018) An overview of blood and plasma supply trends and future developments. PLUS Consensus Conference 2018.

Another key trend has been the move by the fractionation sector to integrate the collection of paid plasma into its operations, thus giving them more control over supply of the key ingredient for PDPs. Source plasma collection costs represents roughly half of the total cost to produce PDPs[38].

Besides the US, commercial source plasma collection centres using paid donors are also located in some EU member states: Germany, Austria, Czech Republic, and Hungary[39]. There is a consistent and significant incremental capacity for plasma collection in those jurisdictions that permit payment of source plasma donors.

Metrics from Canada are aligned with the findings in Table 3.2 which demonstrate the significant difficulty in optimizing the collection of high volumes of source plasma from volunteer donors – H-Q collected 11.4 L/1000 population through its 4 Plasmavie centres in 2016/17 – and CBS collected 6.2L/1000 population. The only 4 countries that are considered 100% self-sufficient in IG are those that had both voluntary and paid donors as seen in Table 3.2[41].

Table 3.2: Per capita plasma collection

Country	Plasma collection L/1000 population[40,41]	IG Self-Sufficiency Ratio (2014)[4]	Plasma Donor Status[40]
United States	66.0	100%	Uncompensated + compensated
Austria	56.6	100%	Uncompensated + compensated
Czech Republic	33.0	100%	Uncompensated + compensated
Germany	31.6	100%	Uncompensated + compensated
Australia[42]	21.5	68%	Uncompensated
Denmark	17.0	81%	Uncompensated
France	16.3	54%	Uncompensated

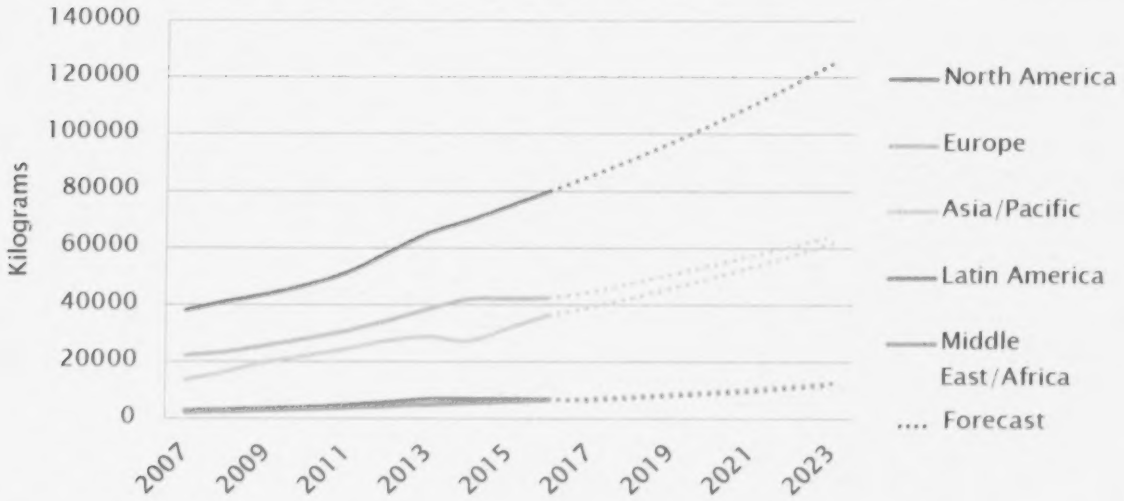
In the US, non-profit blood operators provide the recovered plasma for fractionation but have made very little contribution to the collection of source plasma from their volunteer donors. Since 2008, some US non-profit blood operators have begun to expand volunteer source plasma collection programs with

the goals of both blood donor engagement (e.g. those deferred for travel to a malaria area) and revenue generation from the sale of plasma (see Section 5.3).

Overall, the US supplies 64% of all plasma collected globally and 74% of all source plasma[44]. In 2015, the US supplied 83% of the plasma used to make IG and PDPs for Canadian patients.

The Panel was unable to find any evidence that saturation of the US plasma collection market (i.e. maximum number of plasma donors or source plasma collections has been reached) was a significant risk in the medium term. There were specific geographic regions highlighted in the US where the intensity of plasma collection activity is increasing significantly. In these areas, this concentration of source plasma collection centres drives up competition for plasma donors, which is reflected in the compensation being paid to those donors[45], however, there were no metrics or evidence submitted to the Panel that suggested that saturation was imminent.

Figure 3.4: Global IG Market – Actual and Projected Demand (2007 to 2023)



Data source MRB (2015) Forecast of the Global Immunoglobulin Market (2014–2023)

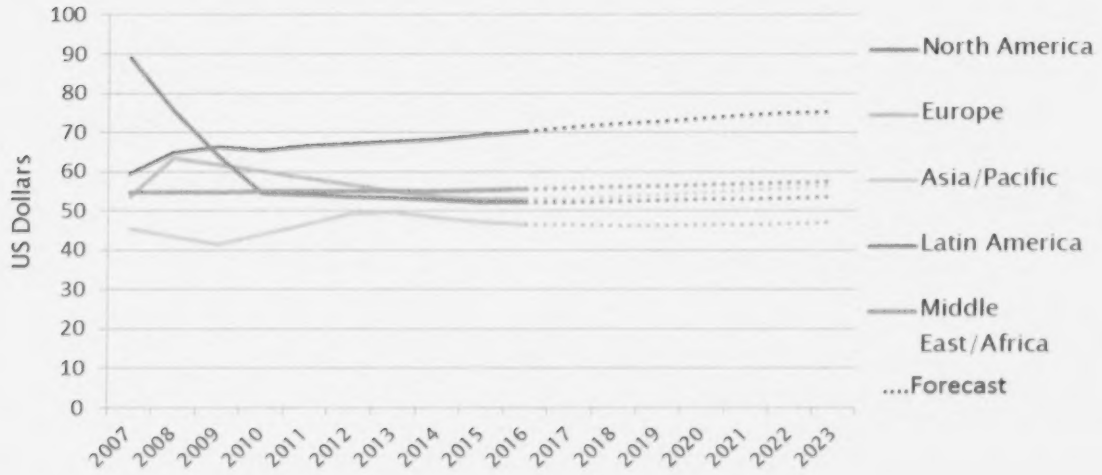
Over the last few years, leaders of the international non-profit plasma industry have called on governments to mitigate the existing risk of dependency on the supply of plasma from any single country or region (see Section 4.2.2).

3.1.3 GLOBAL PLASMA SUPPLY FORECAST

The demand for plasma is projected to increase (Figure 3.4). To meet the demand, planned growth in supply was corroborated by all stakeholders involved in plasma collection and fractionation who met with the Expert Panel.

The data demonstrate a fairly consistent linear growth of demand and supply for IG (and thus source plasma) over the past decades and projected into the future (barring acute supply disruptions) and there has been no evidence to suggest this is likely to change. Similarly, the price of IG is growing and forecast to grow in a linear fashion. The rate of increase in demand/supply of IG has consistently outpaced the rate of increase in the price per gram, due to growing competition among the IG suppliers and to cost containment, particularly in western Europe (Figure 3.5).

Figure 3.5: Global IG Market (Average Sales Price Per Gram)



Data from: MRB (2015) Forecast of the Global Immunoglobulin Market (2014–2023)

3.2 THE FRACTIONATION SECTOR

Plasma collected for the production of PDPs is processed by fractionation companies all around the world - the majority of these are private corporations. Some countries have their own state-owned or non-profit fractionation enterprises, however most jurisdictions purchase the diverse array of PDPs from commercial fractionators.

3.2.1 ACCESS TO FRACTIONATION: CANADA

Canada has had a variety of domestic fractionation facilities in the past, including the Rh Institute Inc. (Winnipeg), and Connaught Laboratories (Toronto). In the 1970s and 1980s the CRC sent its plasma to

these organizations at different times[2]. Since the 1980s, the fractionation industry in Canada has undergone significant change, and both fractionators have since been acquired by private companies.

At this time there are 4 commercial plasma fractionators in Canada at different stages of development:

- Emergent BioSolutions - This company or its predecessors has been a long-time supplier to CBOs of specialty IG products (anti-D) made from paid plasma donors located in Winnipeg, Manitoba.
- Prometic Life Sciences Inc. – This company took over the Winnipeg Rh Institute paid plasma collection activities of its predecessors and has its own fractionation technology and facilities in Canada. It has a plasminogen replacement product under license review by the US Food and Drug Administration (FDA) and Health Canada[46]; and its IVIG is expected to be reviewed by the FDA and Health Canada for an expected commercial launch in June 2019. Its bioseparation technology is distinct from the traditional fractionation process and is expected to provide higher yields of IG per litre of plasma[37].
- Evolve Biologics (a division of Therapure Biopharma) - has albumin and an IG product now in phase 3 clinical trials for PID adult and paediatric patients. It expects to have IG and Albumin on the market by 2021 (with Alpha-1-antitrypsin and other proteins to follow). It also uses innovative technology with enhanced yields of IG expected[47].
- Green Cross Biotherapeutics Inc. (GCBT) – Has opened a new plant in Montreal, Québec that will manufacture IG for the Canadian and US markets, and albumin for the Canadian and Chinese markets[48].This facility will be toll fractionating PDPs for H-Q.

These new or expanding Canadian PDP manufacturers, all of which are regulated and licensed by Health Canada, would likely be eligible to compete for fractionation services and/or sale of commercial PDPs to CBOs when their current contracts expire. While Canada had sent some of its plasma to a domestic fractionator in the 1970s and 1980s, CBOs have not sent plasma to a Canadian fractionator since that time. The emerging Canadian fractionation sector includes promising technological advances that could, if proven safe and effective, significantly increase the yield of IG and other proteins from each litre of plasma (Evolve Biologics and Prometic). Suppliers utilizing high yield technology could enhance the level of Canadian-source PDP self-sufficiency and productivity. Table 3.3 calculates potential self-sufficiency level at hypothetical different increased yields per litre.

Table 3.3: Potential Impact on Self-Sufficiency Level, if Higher Yields Achieved through New Technology (based on 2016/17 figures)

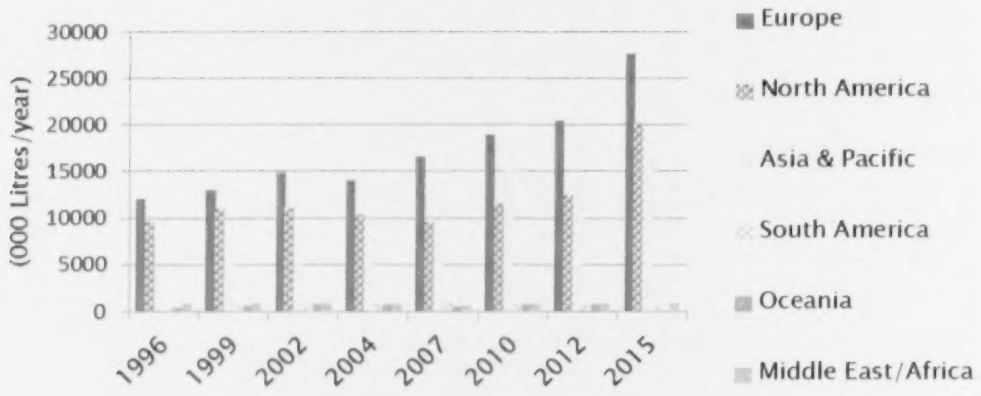
	Potential new self-sufficiency for Canada (%)
Status quo Canadian plasma self-sufficiency	17.0
New Tech 20% increase yield/litre	20.4
New Tech 30% increase yield/litre	22.1
New Tech 40% increase yield/litre	23.8

In 2017, both CBOs hold contracts with commercial fractionators outside of Canada - CSL Behring in Switzerland (CBS and H-Q), and Grifols in the US (CBS)[49] – which are responsible for fractionating

Canadian plasma. These competitive multi-year contracts help assure the availability of PDPs for Canadian patients, provide secure pricing for a range of PDPs, and provide the terms and conditions for toll fractionation.

There is a remote risk of a US Executive Order (for National Defense Resources Preparedness) or a collapse in a US/Canada trade agreement compromising supply of IG or other PDPs but it is very difficult to predict.

Figure 3.6: Global Distribution of Plasma Fractionation Plants and Capacity: Non-Profit and Commercial Organizations



Data from MRB; International Directory of Plasma Fractionators – 2015. February 2017

3.2.2 GLOBAL FRACTIONATION SECTOR – SUPPLY TRENDS

The global distribution of fractionation capacity is illustrated in Figure 3.6: Europe continues to lead the way in total capacity, with overall capacity growing across all regions over the 10 years from 2006 to 2015. Globally, between 1996 and 2015, the total number of commercial and not-for-profit fractionation plants decreased by 9%; however, the global fractionation capacity during the same time has increased by 137%. In other words, there are fewer plants, but these have a greater fractionation capacity.

In the past 4-5 decades, many countries established not-for-profit or state-owned fractionation plants with public funds to meet domestic needs. The following illustrates a range of public or non-profit fractionation arrangements[50]:

Commercial fractionators account for 89% of the fractionation capacity globally[50].

- France, Belgium, and the Netherlands each have their own state or national non-profit fractionators – they purchase volunteer plasma (both recovered and source) from their own national blood operators.
- Other EU member states send their volunteer plasma for toll fractionation by neighbouring non-profit or state fractionators, and/or purchase products from the global market which are largely made from US paid donor plasma.
- The UK has a state fractionator but purchases US commercial plasma for fractionation of PDPs for UK patients due to their country's history with variant CJD (see Section 4.1.2.2).
- Australia is served by CSL Behring, initially a state fractionator that was privatized in 1994 and it is now one of the largest global fractionation companies[50]. Australia collects source and recovered plasma from volunteer donors for fractionation to PDPs by CSL Behring and in addition purchases PDP from the global market to ensure adequate supply to meet patients' needs.

In recent years there has been a significant reduction in the number of non-profit/state owned fractionation plants (particularly in Europe) and overall, the non-profit/state owned sector only fractionates about 10% of global PDPs. Data available to the panel[50] indicated that there continues to be excess capacity in both the commercial and non-profit/state owned fractionation sector globally.

In 2015, the 5 largest commercial fractionators in the world fractionated close to 70% of the global plasma supply[4].

Toll fractionation is part of the overall business model for both the commercial and the non-profit/state-owned fractionation sectors. Currently 5 of the 6 commercial fractionators and most of the large non-profit/state owned fractionators undertake toll fractionation[51] from within their jurisdiction or from other countries. For a commercial manufacturer, this business arrangement is a way to use spare capacity, diversify its revenue stream, and open new markets for its commercial products[51].

3.3 REGULATORY AND LEGAL ENVIRONMENTS FOR PLASMA COLLECTION AND PDPs

3.3.1 CANADA

In Canada, the Minister of Health and Health Canada are responsible for regulating the blood and plasma activities in Canada, which happens under 2 regimes: Blood Regulations for fresh 'raw' components, Food and Drug Regulations for finished products (PDPs).

The Blood Regulations apply to blood and plasma collection and processing activities that occur in Canada. These regulations focus on product safety and take a risk-based approach to regulating the sector. In contrast to the US FDA that sets out explicit specifications that all blood and plasma collection operators must follow, the Canadian approach outlines principles to be followed, then requires a

prospective operator to submit their own proposed detailed procedures when requesting an Authorization. Once granted, that operator is bound to follow the procedures as authorized.

The Food and Drug Regulations apply to all therapeutic drugs, including PDPs. Manufacturers whose PDPs are licensed for sale in Canada are regulated under the Food and Drug Regulations and must meet all requirements applicable to other pharmaceuticals as well as undergo on site evaluations of the manufacturing process including a review of methods to control the process and the quality of the plasma used, as well as the manufacturing processes and viral/pathogen removal/inactivation steps used. For example, regulators would determine whether the plasma had been collected under recognized standards, such as Plasma Protein Therapeutics Association (PPTA) standards. The Food and Drug Regulations also require PDP distributors, including the CBOs, to hold a distribution license.

Both sets of regulations set out reporting responsibilities related to errors, accidents, and adverse reactions to ensure product safety. Under the Blood Regulations, all suspected errors or accidents identified after the distribution of the plasma must be reported to Health Canada if there is a reasonable probability that these could lead to a serious adverse reaction. Under the Food and Drug Regulations, when manufacturers become aware of any serious adverse drug reaction occurring in Canada, and any serious unexpected adverse drug reaction that has occurred outside of Canada, they must report it.

Both sets of regulations set out some reporting responsibilities related to errors, accidents, and adverse reactions, but they vary as set out in Table 3.4.

The timeframe for reporting incidents depends on the severity of the incident (e.g. a reaction resulting in death must be reported within 24 hours). In addition, blood/plasma collectors must file annual summary reports of all above errors, accidents, and adverse reactions. Licensed PDP manufacturers must file annual summary reports of all global adverse reactions including infectious disease transmission. Health Canada must complete its review of these reports within 60 days of receipt. Federal post-market surveillance activities also include a lot release program for PDPs.

Surveillance of blood-borne pathogens in the general population is the responsibility of PTs, each with their specific legislation that mandates reporting of specific diseases to public health officials. These laws do not uniformly require that case reports include the individual's history as a blood/plasma donor or recipient. For example, Ontario reports of vCJD cases must specify whether the person had given blood/plasma or received blood/PDPs, while hepatitis B virus (HBV)/HCV cases do not specifically ask for this[52]. Sharing of surveillance data by PTs with Health Canada and the Public Health Agency of Canada is done on a voluntary basis through data sharing agreements. The Public Health Agency of Canada maintains a national summary of disease case reports in the general population[53] and also produces

more detailed reports on disease-specific surveillance systems including blood-borne pathogens such as HBV and HCV, HIV, and others[54,55].

TABLE 3.4: Summary of Federally Reportable PDP-Relevant Errors, Accidents and Adverse Reactions

Incident Type	Person Affected	Who Reports	Who Receives Report Federally
Error or accident – plasma for manufacturing (re: product quality only)	PDP recipient (if PDP had been used)	Licensed collector	**Mandatory**: to Blood regulator (Health Canada)
Error or accident – PDP	PDP recipient (if PDP had been used)	Participating hospitals (10% participate in TESS, as sentinel system)	**Voluntary**: PT submits reported (blood or PDP) transfusion-related error/accident data annually to PHAC.(TESS)
Serious or unexpected adverse reaction from donation of blood or plasma	Donor	Medical Director of licensed collector is responsible for donor health – any duties are as physician to their PT	
Serious or unexpected adverse reaction from use of PDP	PDP Recipient	PDP manufacturers, "if made aware" of adverse reaction	**Mandatory**: to Food and Drug regulator (Health Canada)
		Participating hospitals (approximately 90% of hospitals providing transfusion services participate in TTISS)	**Voluntary**: PT submits reported adverse reaction data to PHAC on an annual basis (TTISS)
		Hospital blood bank/ pharmacy (PDP distributor)	**Voluntary**: to distributor, manufacturer, and regulatory authorities (CSA Standard s14)
		Pending (Vanessa's Law passed 2014; regulations not yet in effect): Hospital / end user	**To be Mandatory**: to whom is still TBD

Errors and accidents: Such events are those that could compromise human or blood safety and are (error) or are not (accident) attributable to deviations from procedure or law.

Serious or unexpected adverse reactions: A "serious" reaction involves a define level of seriousness (e.g. requiring medical intervention, or death), while an "unexpected" reaction means it was not an expected side effect. Such adverse reactions in donors and recipients are reportable to Health Canada.

TESS: Transfusion Error Surveillance System (see below)
TTISS: Transfusion Transmitted Injury Surveillance System (see below)

Surveillance of cases of blood-borne pathogens transmitted by blood or PDPs is also the mandate of PT jurisdictions and sharing of this data nationally is through the voluntary submission of data to the national Transfusion Transmitted Injury and Transfusion Error Surveillance Systems (TTISS, TESS) which were established in the wake of the Krever report[2]. PTs submit data to Public Health Agency of Canada annually (approximately 12 months in arrears). CBS and H-Q are stakeholders who submit data and receive reports. National reports on PDP and transfusion incidents are published and posted online. The most recent data available online are from 2013; the 2015 data have been shared with PTs and stakeholders and will be posted online in time[55].

Currently, the Public Health Agency of Canada provides some technical support to enable input of data by PTs into the Canadian Network for Public Health Intelligence database from which annual national reports are prepared. Public Health Agency of Canada also contributes Canadian data to the International Surveillance of Transfusion-Associated Reactions and Events (ISTARE) on request – 1 submission was made in 2017.

There is no regulatory requirement for CBOs to routinely submit seroprevalence rates for their blood donors to federal authorities, however CBS has published annual Surveillance Reports[56] since 2012 and H-Q includes positive test result data in its Annual Reports[57]. Under certain circumstances, Health Canada may require donor testing results to be reported under a "regulatory authorization" where specific terms and conditions are applied. If the Minister of Health later determines that there is no longer a need for the requirement it can be withdrawn. An example of this would be reporting requirements related to the recent change to the blood donor deferral policy related to men who have sex with men in June 2016. Since 2016, both CBOs have been required to annually report the number of positive unit test results for certain infectious disease markers and an assessment of potential emerging disease pathogens as part of their post-implementation monitoring plans. The reports are received and formally reviewed within timelines set internally. Health Canada does not publish them.

In addition to regulatory requirements, the fractionation industry through PPTA has a robust quality program (Quality Standards of Excellence, Assurance and Leadership (QSEAL)/International Quality Plasma Program (IQPP) certification) that sets voluntary standards, as seen in 4.1.1. All certificants of this program (which includes plasma collection centres such as CPR, but not CBS) are required to submit all reactive infectious disease test results to the National Donor Deferral Registry[58] , as well as to report all such test results to PPTA on a quarterly basis. If those results exceed published PPTA alert limits, the PPTA monitoring system triggers follow up remedial action and monitoring.

3.3.2 INTERNATIONAL REGULATORY REGIMES

There are differing international regulatory regimes in addition to voluntary industry standards for monitoring and ensuring safety in regard to source plasma. Depending on the different markets for their products, fractionators around the world often have to comply with multiple regimes.

Generally both Canada and the US rely on voluntary reporting of donor seroprevalence rates by CBOs and other licensed plasma collectors, as seen in Section 4.3.1. The EU has a more proactive mandatory regime where each collection centre must report donor seroprevalence rates and any deviation from established rates requires followup, explanation and intervention by the operator if needed[59]. The more stringent regulatory requirements of some jurisdictions and voluntary industry standards in the fractionation industry have allowed the collection and sharing of data which allow further insight into the issue of the relative safety of paid and volunteer donors. This is discussed in detail in Chapter 4 (see Section 4.1.2).

3.3.3 SOURCE PLASMA DONOR SAFETY

In Canada the CSA Standards provide guidance for plasma volumes collectible by source donor weight, protein levels, frequency of collection and total annual volume limits. Beyond this, donor safety is the responsibility of the CBO or commercial operator of plasma centres. There is no specific federal oversight of plasma donor safety other than incidents otherwise reportable related to the safety of the product.

In spite of the major role of US plasma in the production of much of the global supply of IG, regulations governing the collection of plasma for manufacturing IG and other PDPs have not been harmonized between the US and Council of Europe. As an example, there are some 20 differences in criteria applicable to whole blood donors (recovered plasma) when comparing US to Council of Europe regulations[60]. Even amongst European countries the regulations are not aligned (Table 3.5).

Table 3.5: Apheresis Plasma Collection Regulations: Examples of Regulatory Differences in EU[61]

Regulatory	Frequency	Collection Volume
Council of Europe Recommendation No R(95) 15	≤ 33/year ≥ 48 h between	≤ 16% TBV and ≤ 750 ml# (unless replacement) ≤ 25 litres/year
National Authorities		
France	≤ 24/year ≥ 2 wk. between	≤ 750 ml/donation (≤ 16% TBV)
Germany	2x/week; ≥ 48 h between ≤ 45/year	≤ 850 ml*/donation (if ≥ 176 lbs) ≤ 28.5 litres/year

*** = Including anticoagulant; # = Excluding anticoagulant**

3.3.4 LEGISLATION – PLASMA SOURCE DONOR COMPENSATION

Further complicating the rather incoherent regulatory framework in the plasma sector, there are also mixed public policies and legislative approaches across jurisdictions related to compensation of source plasma donors:

- some countries prohibit any payment of plasma donors and require all donors to be volunteer;
- some countries strongly encourage volunteer donors but allow compensation up to a maximum amount;
- some countries allow payment of both blood and plasma donors;
- some countries prohibit payment of donors as well as the import of PDPs produced from plasma from paid donors; (for example, France unless imported PDPs meet specific criteria)[62].

France[63], Belgium[64], and the Netherlands[65] are examples of countries that have entrenched voluntary donation within national legislation.

Canada is even more complex with varying regimes across the provinces:

- Québec prohibits payment for any body part, including blood or plasma;
- Ontario and Alberta prohibit offering or accepting payment for giving blood or plasma, but CBS is exempt from this prohibition;
- the remaining provincial territorial jurisdictions have no legislation on this issue.

CHAPTER 4

SECURE AND SUSTAINABLE SUPPLY OF PDPs AND BLOOD FOR CANADIANS

A number of key elements are included in the concept of security and sustainability of the supply of IG and other PDPs including:

- Safety – of the PDPs used to treat patients;
- Availability – a sufficient supply for patients, the ability to respond to the pressures of long term growth as well as deal with acute shortages. From a patient perspective, ensuring the availability of a secure and sustainable supply of PDPs is also considered a safety issue[66];
- Affordability – for both patients and taxpayers. Cost-efficiency and feasibility are factors in this regard.

This chapter reviews each of the above elements. The question of whether plasma collection activities are detrimentally affecting blood collections is also explored.

4.1 SAFETY OF PDPs

Three decades ago, the crisis of HIV and HCV contaminating the blood supply, which in Canada culminated in the Krever Commission's findings, had a major impact on all parts of the supply chain of plasma and the production of PDPs globally. That global tragedy resulted in a significant overhaul of legislation and regulation, systems and processes involved in screening and testing blood and plasma donors and their donations, the handling of plasma for fractionation, and the manufacturing processes involved in the production of PDPs. The outcome of these changes has been dramatic: **there have been no confirmed cases of disease transmitted through PDPs in over 2 decades**[67](Note the vCJD crisis in the UK will be discussed below).

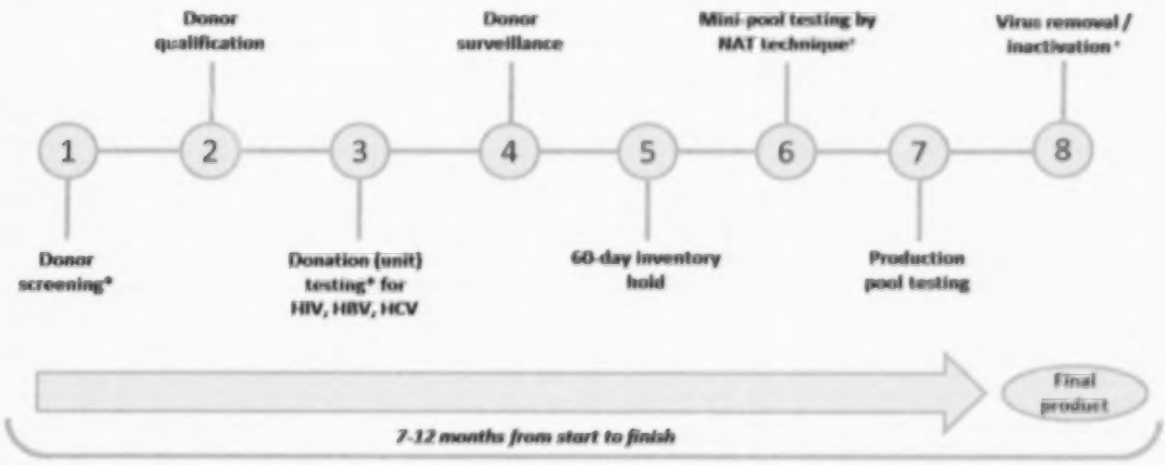
This remarkable outcome is the result of ongoing rigorous surveillance and regulation by government agencies; collaboration and coordinated efforts amongst academics and scientists in the fields of transfusion medicine, infectious disease and public health; ongoing and continuously evolving quality programs amongst blood operators and their national and international associations American Association of Blood Banks, International Society of Blood Transfusion (ISBT),etc.; non-profit and for

profit fractionators and their respective associations (PPTA, IPFA); and national regulators. See Figure 4.1 for key steps involved in keeping plasma products safe.

4.1.1 STEPS TO PROTECT PDP SAFETY

Current measures ensuring the safety of IG and PDPs are based on a multi-pronged approach. Many of these steps are embedded in regulation and legislation and apply to all plasma donors, volunteer or paid, as well as those agencies and facilities collecting and processing plasma to make PDPs. In addition industry associations have developed voluntary quality programs (QSEAL and IQPP standards in particular) which call for requirements beyond regulations. The QSEAL Program provides independent certification of adherence by fractionators to the voluntary standards related to collection, processing and testing of source plasma. The IQPP certification focuses on Donor Management, Donor Health, and Center Management[68,69]. These standards are used to certify plasma collection sites and further ensure the safety of source and recovered plasma used in the fractionation process, as well as protect the safety of plasma donors as seen in Section 3.3.3.

Figure 4.1: Key Processes for Ensuring Safety of PDPs



* regulation ° regulatory guidance; voluntary standard

Figure 4.1 illustrates the steps which apply to source plasma collected in the US which is the raw material in most PDPs used in Canada. Canadian practices are similar in most cases; significant differences are noted where applicable. PPTA voluntary standards apply to plasma collection agencies and manufacturers certified by PPTA. Key steps which have been put in place to ensure PDP and plasma donor safety include:

1. **Donor screening**[70](regulatory) – Plasma collectors screen each donor against established eligibility criteria designed to identify potential risks through a physical exam, interview and questionnaire. For collection agencies certified by PPTA, prospective donor names are also checked against the (US) National Donor Deferral Registry. Plasma/blood will not be drawn from

those who do not pass these donor screening steps or whose names appear in the National Donor Deferral Registry. Regulations require that qualifying medical exams, repeated annually, be conducted on all source plasma donors donating at intervals of less than 30 days[70]. Those who donate at intervals >30 days do not require a medical exam[70].

2. **Donor qualification**[68](voluntary standard) – On a first visit, a prospective source plasma donor undergoes initial screening described above. If they pass, a sample or unit drawn at that visit is fully tested but not sent for manufacturing. Only after a donor donates again within 6 months and again passes all tests are they qualified to have donations used for manufacturing.
3. **Donation (unit) testing** (regulatory) – After collection, each plasma unit is tested for viral markers for HIV- 1 and HIV-2, HCV, and HBV. Not all tests performed on whole blood for transfusion are needed for PDP manufacturing as some blood-borne pathogens (human T lymphotropic virus (HTLV), West Nile Virus, and Chagas disease)[71] are found only in cells, not plasma.
4. **Donor surveillance** (voluntary standard): All plasma collectors certified under the PPTA IQPP standards must routinely submit all seroprevalence data on their donors to the PPTA. Each plasma collection centre's test results are monitored to track local infection seroprevalence rates and are investigated if above the stated thresholds[68].
5. **60-day inventory hold**[69](voluntary standard) – Under PPTA standards, every source plasma unit for manufacturing is held in inventory for at least 60 days post-donation (so it can be retrieved before being sent for processing if an issue is found with the subsequent donation). The 60 day hold does not apply to plasma received for toll fractionation.
6. **Mini-pool testing by nucleic acid amplification technique** (NAT) (regulatory guidance; voluntary standard[69,72]) – For the manufacture of PDPs, thousands of units of donated plasma are combined into 1 large pool of plasma which is then processed. Prior to this, mini-pools are created (CBOs use 6 units per pool) and these undergo a highly sensitive form of testing (NAT testing) for HIV, HCV and HBV[73]. This step can detect virus at lower levels than the routine screening tests.
7. **Production pool testing** (voluntary standard) – Before processing, large pools (thousands of units) of plasma are created and are again tested for HIV, HCV, HBV as well as for Parvovirus B19 and hepatitis A[69].
8. **Virus/pathogen removal / inactivation** (regulatory guidance; voluntary standard) – multiple steps are employed. Each step focuses on 1 or more risks such as enveloped viruses (e.g. HIV, HBV, HCV), non-enveloped viruses (hepatitis A virus, hepatitis E virus, human parvovirus B19), bacteria, and prions (e.g. vCJD). The combination of methods used varies by product allowing the removal/inactivation of pathogens without destroying the therapeutic effectiveness of the

product[74,75]. Modern processes used to remove/inactivate infectious material during manufacture include steps such as:

- treatment with solvent detergent
- pasteurization
- low pH treatment
- viral filtration (nanofiltration)
- vapour heat of lyophilised products
- dry heat treatment of lyophilised products[76]

As noted above, the multiple safety steps and ongoing oversight and surveillance by various agencies have resulted in an impressive safety record for PDPs with no confirmed case of transmission of infectious disease by PDPs in over 20 years[67]. Further technological safety advancements continue to be developed. For example, technology to reduce pathogens in plasma utilized for direct transfusion has been approved for use by the US FDA[77]; future use of such plasma in manufacturing could be possible at a later stage.

4.1.2 PRODUCT SAFETY – PAID PLASMA DONORS VERSUS VOLUNTEER PLASMA DONORS

In spite of the consistent track record of safety of PDPs made from both paid and voluntary plasma donors over the last 20 years, the concern over whether payment of source plasma donors constitutes a threat to the safety of PDPs remains an issue repeatedly articulated by some stakeholders.

To further examine the issue, the Panel reviewed available data on seroprevalence of blood-borne pathogens across the 2 groups of donors. Analyses of donor data sets based on the reporting required by the EU (see Section 3.3.2) were discussed at an international IPFA conference in September 2017. One analysis compared 2 large data sets from 2013-2016 of infectious disease screening test results on source plasma from qualified, paid US source plasma donors (25.7M units) and recovered plasma from volunteer US whole blood donors (1.8M units). The data show no statistically significant difference in repeat reactive rates for hepatitis B virus surface antigen (HBsAg), HIV, or HCV across the 2 populations. In a different analysis using NAT test results for HCV, HIV, and HBV, 2M source plasma (paid) donations were compared to 136,000 whole blood (volunteer) donations from Jan – May 2017, again without statistically significant differences in the prevalence of viral markers[78]. These data fail to demonstrate any discernible difference in the prevalence of infectious disease markers between plasma donations from qualified paid source plasma donors and plasma from volunteer whole blood donors in the US.

A donation in the window period (early in the infection of a donor with a virus, before any testing becomes positive) constitutes the major risk of viruses entering the fractionation process. The viruses of known concern are HCV, HIV, and HBV. The residual risk is the estimated probability of a potentially infectious plasma unit entering the manufacturing pool[67]. The calculation of residual risk is used to assess the impact of industry safety initiatives and can be used to estimate the viral load in plasma pools. Because of the step-wise processes for ensuring safety, any contaminated units would have detection levels below that of the NAT test, and that residual risk of transmission is reduced to zero by viral removal and/or inactivation processes. The 60 day inventory hold is an additional step which helps

to eliminate any residual risk of a window period donation by requiring a negative result on a subsequent donation in order to release the unit on hold.

According to a December 2017 US FDA Guidance document, the residual risks of screened human blood and blood component donations were estimated to be 1 in 1,467,000 donations for HIV-1, and 1 in 1,149,000 for HCV (2007/2008)[72]. Studies of Canadian blood donors estimate residual risks to be comparatively lower than whole blood donors in the US[79].

4.1.3 EMERGING RISKS TO PLASMA SAFETY

While the safety steps which are described in detail above were established to address a number of known risks, stakeholders also have concerns that new blood-borne pathogens continue to emerge.

As noted above, since the crisis of the 1980s with HCV and HIV, in addition to government regulators, advisory committees to regulators, and public health agencies, there has been sustained work by scientific associations such as the ISBT and American Association of Blood Banks, the fractionation industry (PPTA and IPFA), in conjunction with blood operators to undertake environmental scans, early identification and research on emerging infectious threats to the blood supply. The overall goal is to ensure that regulators, industry and operators respond nimbly and appropriately to any emerging threat, crafting new safeguards, guidelines and regulation to protect the public.

Examples of 2 recent or emerging pathogens, hepatitis E (HEV) and vCJD, are included below to illustrate the work involved when the risk of transmission of a new agent is a concern. Under similar processes, 2 recent pathogens - West Nile and Zika viruses - were found not to be significant risks for transmission by PDPs due to the fact that existing viral inactivation mechanisms were found to be effective in protecting the safety of PDPs so no additional measures were needed for plasma for manufacturing, though extra measures were needed to protect safety of fresh blood components[80].

4.1.3.1 Hepatitis E

Hepatitis E is an emerging enteric (intestinal) non-enveloped virus with several strains that can cause acute or chronic hepatitis in humans. Transfusion-related cases have been documented in several countries including the UK and France[81,82]. A recent study of approximately 14,000 Canadian voluntary whole blood donors (July 2013- December 15 data) demonstrated an overall prevalence rate of 5.9% in the Canadian blood donor population[83]. Consistent with this, HEV was detected in 8 of 75 plasma pools from Europe and the US[81]. To date, there is no test appropriate or feasible for screening donors nor any methodology or questions which would effectively identify donors at risk for HEV.

In 2015, CSL Behring conducted the first large-scale survey of the prevalence of HEV infection in US paid plasma donors: 3 of 128,020 donations (0.002%) collected from 96 sites were positive for HEV[84]. This study suggests that for the population of donors studied, the contamination of plasma pools with HEV would be at a very low rate, lower than the US population seroprevalence rates[85] documented above, suggesting that the various screening and testing regimes for source plasma donors are likely quite effective, even if not specific, for HEV[84].

Some European blood donor communities show a higher seroprevalence rate (e.g. 27% in the Netherlands)[84]. In January 2015, following an assessment of prevalence rates and some unique characteristics of HEV, the European Medicine Agency added HEV ribonucleic acid (RNA) testing of plasma pools as an additional safety measure required under their regulation[81,82].

Recent studies have demonstrated that current PDP viral removal or inactivation effective against non-enveloped viruses are also effective against HEV[86]. For fresh blood components, however, HEV remains an emerging concern[87].

4.1.3.2 Prion Diseases

Creutzfeldt-Jakob Disease (CJD) is a rare and transmissible neurodegenerative disease caused by a prion protein. In 1996, the UK identified a previously unrecognized variant of CJD (vCJD). Transmission was associated with having been exposed to contaminated beef, and over time the UK reported a total of 4 transmissions of vCJD infection by transfusions of red cells and one *possible* transmission of vCJD by a PDP[88].

In the latter case, evidence of vCJD infection was found post-mortem in a hemophilia patient who had been treated in 1994 and 1996 with human UK-plasma-derived Factor VIII that contained plasma from a donor who later developed vCJD[89]. This is the only report where vCJD has been found in a patient with hemophilia or any patient treated with plasma products. PDPs have not been implicated in vCJD transmission in any other case.

As a result, even though there are no other reported cases of vCJD transmitted by PDPs, UK plasma is currently not used either by the state fractionator in UK or by global fractionators for manufacturing PDPs. There is evidence that steps taken during plasma fractionation can reduce or eliminate the risk of transmission of vCJD[90]. Even so, WHO and European Medicines Agency Guidelines recommend the recall of PDPs made with blood or plasma from individuals subsequently recognized as having vCJD[90,91], and no PDPs distributed in Canada are made from European plasma (only US and Canadian plasma).

Since 1999, to reduce the risk of vCJD in the blood supply, the US FDA has issued guidance documents recommending that donors who had spent time in certain countries where the risk of dietary exposure to the bovine spongiform encephalopathy (BSE) agent was higher than that in the US be deferred from giving blood[88]. Other countries, including Canada, adopted and continue to update similar measures to screen out donors considered to be at increased risk of vCJD, i.e. those who resided in the UK or other risk areas within specific time periods[92,93]. The US FDA guidelines are currently under revision and may

soon be amended to lift some restrictions on donors who have spent time in certain European countries[88,94].

Canada continues to monitor the level of vCJD risk through the Canadian Creutzfeldt-Jakob Disease Surveillance System operated by the Public Health Agency of Canada. All human prion diseases, including vCJD, are provincially reportable and nationally notifiable[95]. Canadian prevalence rates of vCJD are extremely low (total of 2 cases of definite or probable vCJD deaths in Canada 1994-2017)[95]. No cases of transfusion-transmitted vCJD have been reported in Canada or the US.

4.2 SECURITY AND SUSTAINABILITY OF SUPPLY OF PLASMA

On the issue of security and sustainability of the supply of IG and other PDPs, the concept of jurisdictional self-sufficiency in the supply of plasma, which is the key raw material, is the topic of much discussion globally by patient groups, governments, blood operators, fractionators and the many organizations which represent the blood sector.

4.2.1 PLASMA SELF-SUFFICIENCY – CANADA

The meaning and importance of self-sufficiency in relation to plasma needed for the manufacture of PDPs have been debated in Canada for decades. In 1976 the Canadian Blood Committee and the CRC Blood Transfusion Services endorsed 3 principles for the national transfusion service: protection of the system of voluntary donation, national self-sufficiency in blood products, and gratuity of blood products to recipients[2]. In the late 1990s, Commissioner Krever reiterated these principles based on the following rationale:

- Canadian donors would be relatively safer than paid donors given their altruism, lower infectious disease rates, access to health care, and regulatory control over donor screening, collection and plasma processing;
- The plasma supply in Canada would not be affected by shortages on the world market;
- Canada would have time to take precautionary action if a blood-borne pathogen were to emerge in another country[2].

Since the Krever Commission, various actions have been taken by CBOs toward the goal of self-sufficiency in order to meet domestic needs:

- 2004 – CBS set a target of 40% self-sufficiency for producing IG from Canadian, based on stakeholder consultations;

- 2006 – H-Q set a target of 30-40% self-sufficiency for producing IG from Québec plasma, based on a consensus forum that prioritized patients with immunodeficiency;
- 2009 – CBS lowered its IG self-sufficiency target to 28-30% having reduced the risk of a supply disruption by having 2 separate fractionators under contract;
- 2012 – CBS closed its Thunder Bay stand-alone apheresis plasma collection centre due to high costs and difficulty finding physicians to undertake the required medical examination of donors;
- 2014 –At the start of its Plasmavie initiative, H-Q reframed its target to be a collection volume of 200K litres per year of source plasma to cover the needs of patients with PID and SID, which represented approximately 30% IG self-sufficiency;
- In 2016-17 CBS remained at 17% self-sufficiency for plasma for IG, of which >15% was from recovered plasma and < 1% from Canadian apheresis plasma[35,96]. The business plan currently being considered by CBS for expansion of source plasma collection in Canada proposes a target of 50% self-sufficiency for IG based on a rationale of ensuring adequate plasma for 4 priority patient groups: PID, CIDP, ITP and MG. (The Panel notes that CBS's calculation included patient groups beyond those considered "priority" in the UK framework, notably all ITP uses.);
- In January 2018 H-Q reduced its collection target from 200K to 150K litres per year which could be used to produce 675,000g of IVIG (current demand (2015/16) for patients with PID and SID 405,000g). In 2016/17, H-Q collected approximately 44,000L total from the 4 Plasmavie centres, and the total source plasma and recovered plasma sent for fractionation in 2016-17 was >95,000L[96].

The differences in CBS's and H-Q's approaches to defining and setting self-sufficiency objectives and priority conditions reflect a broader international phenomenon: although there is broad support for the concept of self-sufficiency, there is no consensus on how to interpret and apply it in practice. Furthermore, based on the utilization metrics highlighted in Chapter 2, managing demand for IG could also play a significant role in achieving a higher level of self-sufficiency – for example, in 2014, the UK used 53% of the IG used by Canada, per capita[97]. If Canadian IG utilization rates matched those of the UK, Canadian plasma collection levels would already be at 35.9% self-sufficiency instead of 17%.

Despite the modest levels of Canadian source plasma collection to date, both CBOs have demonstrated that their procurement practices for IG and PDPs have been a key enabler of their ability to sustain and secure an adequate and affordable supply of IG and other PDPs over the last 20 years. Contractual mechanisms to protect inventory levels combined with regulatory mechanisms to facilitate product import and approvals are important contributors to security of supply.

4.2.2 PLASMA SELF-SUFFICIENCY – INTERNATIONAL

Internationally over the last 20 years, there has been and continues to be a strong push for jurisdictions to collect more plasma within their home jurisdictions to meet the needs of their citizens. Particularly given that the US supplies 64% of all plasma (source and recovered) for manufacturing PDPs and 74% of all source plasma collected globally, both the IPFA and PPTA are asking countries to increase their levels of domestic plasma collection[98].

An important tension in pursuing such a goal is the feasibility challenge of reaching self-sufficiency in the context of the long-standing public policy preference for using voluntary donors.

Building on the 2009 Melbourne Declaration[99], in 2010 the World Health Organization (WHO) collaborated with the International Federation of Red Cross and Red Crescent Societies in publishing *Towards 100% Voluntary Blood Donation - A Global Framework for Action*[100]. In the same year, a World Health Assembly resolution urged member states "to take all the necessary steps to establish, implement and support nationally-coordinated, efficiently-managed and sustainable blood and plasma programmes according to the availability of resources, with the aim of achieving self-sufficiency, unless special circumstances preclude it".[101]

In 2013, under the auspices of the WHO, The Rome Declaration on Achieving Self-Sufficiency in Safe Blood and Blood Products, based on Voluntary Non-Remunerated Donation[102] recommended that national authorities introduce legislation to prohibit donor remuneration and phase out PDPs derived from remunerated donors. However, based on the projected threat to global PDP supplies if this were implemented, networks of patient groups and both the non-profit and commercial plasma industry associations took strong exception to that recommendation[103]. That concern had previously been expressed in the 2002 position statement by EU regulatory authorities: "a requirement for [voluntary] donors would create major supply problems and product shortages without any justification on grounds of safety".[104]

The European Council Directive 2002/98/EC is the legal framework for quality and safety standards for blood and components throughout the transfusion process. Its Article 20 calls on Member States to "take all necessary measures to promote Community Self-Sufficiency in human blood or human plasma", and for this purpose, to "encourage the voluntary unpaid donation of blood and plasma".[105,106]

A 2015 report commissioned by the European Commission's Executive Agency for Health and Consumers drew from extensive 2012 surveys of relevant EU blood and plasma stakeholders and other sources[107]. A key challenge identified included a lack of a common understanding of 'self-sufficiency' and its geographic scope (i.e. national vs. regional).

In 2016, Strengers (of IPFA) and Klein wrote about plasma as a *strategic resource* as defined by the EU: "economically important raw materials which are subject to a higher risk of supply interruption". The authors supported a multi-pronged approach to achieving a secure and sustainable supply including mitigating the risk of shortages through multiple strategies for assuring access to fractionated products which are needed to meet patient needs in a timely manner. In this approach the authors assert that "strategic independence" is the goal that countries should strive to achieve rather than 100% self-sufficiency which is not realistically achievable for all countries[108].

The perspective of patients dependent on PDPs has been formalized through recommendations coming from a series of multi-stakeholder conferences organized by PDP-dependent patient groups (Dublin Consensus Statements 2010, 2011, and 2012)[66,109,110]. The recommendations outline the criticality of optimizing the supply of PDPs, noting that PDPs made from both paid and volunteer donors are currently essential to meet global health needs, and **the major risk to safety for patients is an insufficient supply of PDPs versus any perceived safety risk associated with paid donors.** This global view aligns with the input provided to the panel by organizations representing Canadian patients who are dependent on PDPs as well as clinician groups providing care to those patients. (Their input is summarized in Chapter 5, and see Appendices D and E).

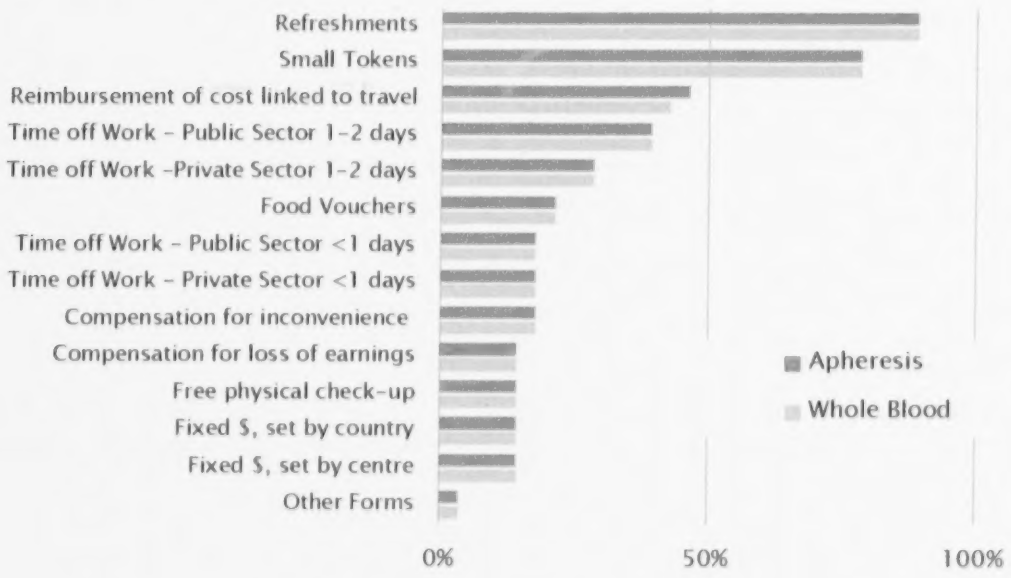
Like Canada, the majority of EU Member States and many other developed countries are unable to meet their needs for IG and other PDPs using voluntary donations and therefore depend on importing PDPs made from paid donors to meet the health needs of their citizens. As noted in Chapter 3, only 3 European states achieve 100% self-sufficiency (Germany, Czech Republic, and Austria) and all depend on both voluntary and paid plasma donors within their jurisdiction.

4.2.2.1 Voluntary and Paid Donors – International

To further complicate things, over the last 2 decades there has been an evolving continuum of donor compensation, incentives, and rewards in the voluntary donor sector. There is no longer a clear delineation between a "volunteer" donor and a "paid" donor. In the global non-profit blood operator community, a wide array of monetary and non-monetary incentives have been developed to recruit and sustain blood and/or plasma donors – these incentives include cash payments, vouchers, discount coupons, gifts, event tickets, health checks, or time off work[111]. In the US, an FDA compliance guidance document in effect since 2002 describes the types of incentives used for blood donors, and provides examples of when these would be considered "paid" versus "volunteer" donations. If paid, certain labeling requirements apply to components for transfusion only[112]. In 2014, 13 European countries had formal laws or binding recommendations that sets out what types of donor compensation or payment is allowed[105].

Survey results from 2014 document the variety of monetary and non-monetary *incentives* in use for volunteer apheresis plasma and/or blood donors in Europe (Figure 4.2). The fixed sums offered to volunteer blood and plasma donors ranged from 16-30 Euros in the countries where donor payment was allowed (Germany, Czech Republic, and Austria), while the Netherlands, offers a 20 Euros incentive to reimburse travel costs to volunteer donors. In addition, of 28 respondent EU countries, 11 offer 1 or 2 full days off work for both blood and plasma donations, yet only 3 of those countries consider these benefits an incentive / payment for the volunteer donor[105]. Some argue that it is incongruous that such high-value practices are not considered forms of payment[111].

Figure 4.2: Occurrence of compensation practices



Graph from data European Commission Staff Working Document on the implementation of the principle of voluntary and unpaid donation for human blood and blood components as foreseen in Directive 2002/98/EC/(2016). Brussels, 21.04.2016. SWD (2016) 130 Final.

However, the impact of increasing incentives for donors is clear as demonstrated in Table 3.2 (Chapter 3) where it can be seen that European countries which permit monetary compensation of source plasma donors have a significantly higher per capita yield of source plasma collection than those jurisdictions which do not permit this.

In summary, it is important to recognize that over the last 2 decades, recruitment/reimbursement incentives for volunteer donors have evolved and in some instances are now overlapping with paid plasma donors, in part reflecting the challenges of sustaining an adequate number of donors to meet public need for blood and blood products.

4.3 MOVING TO PLASMA/PDP SELF-SUFFICIENCY: COST AND FEASIBILITY ISSUES

As noted above, there is no one definition of self-sufficiency and in jurisdictions where self-sufficiency has been a public policy goal, different rationales and targets for plasma collection have been set, ranging from:

- the ability to meet the needs of those patients whose survival depends on the availability of the product (PID);
- the ability to meet the needs of all citizens for PDPs. The Netherlands provides an active example of this approach, with a national self-sufficiency goal in legislation[65];
- a goal which sets volume targets based on a balanced appraisal of the cost and feasibility of collection of volunteer plasma within the jurisdiction. Belgium for example has a legislated target of 50% of the volume required to meet IG needs and 100% for albumin[113]. The Australian NBA sets the blood operator's plasma collection volume targets annually (historic volume targets have achieved the following levels of self-sufficiency: 68% in 2013/14; 60% in 2014/15; 57% in 2016/17)[42].

In most countries where some degree of plasma self-sufficiency is targeted through policy or legislation, blood operators contract with state, nonprofit or commercial fractionation partners within or outside the jurisdiction (toll fractionation) to ensure the return of derived products to patients within the jurisdiction. This approach is then combined as needed with the purchase of commercial products (usually through competitively procured contracts with commercial fractionators) to meet the total needs of their public.

The global metrics available within the last 6 years show the overwhelming challenge facing jurisdictions attempting to achieve some level of self-sufficiency with volunteer donors. In 2015, only 11% of the global source plasma supply comes from volunteer donors and the balance(89%) is from remunerated donors[50].

Based on evidence and expert input from within Canada and internationally, it seems clear that public or non-profit sector source plasma programs based on voluntary donors are less efficient and much more costly than commercial plasma collection centres utilizing paid donors. In addition, from interviews with both CBOs and industry representatives, timelines for scale-up and reaching optimal collection volumes also differ. The commercial operators target scale-up within 24 months and are also able to optimize sustained donor commitment over time. After 4 years of Plasmavie activity, H-Q in 2018 reduced its collection target from 200,000 litres of source plasma to 150,000 litres (a 25% reduction) and indicated to the Panel that it would take 10 years and a high cost to achieve its original target. CBS has also indicated that their scale up to 50% self-sufficiency would take longer than would be the case with commercial operators and would be significantly more expensive than the cost of purchasing PDPs on the market. Different sources suggest that enhancing self-sufficiency through the collection of volunteer apheresis plasma by the blood service would seem to cost 2 to 4 times as much as that collected by

commercial industry[36,114]. In part this relates to the limits on donation frequency which appear to be inherent in a volunteer donor based source plasma operation – for example: a commercial operator in the US achieves an average paid plasma donor frequency of 17.3 donations per year[115] while non-profit operators across Canada, the US, the EU and Australia average from 4-7 source plasma donations per year per volunteer donor[116,117,96,61,118,119]. The collection volumes per source plasma collection site run by non-profit operators range from 4,000 – 15,000 litres in Canada and the EU[119], while in the US and EU commercial sector the volumes per site range from 40,000 to 50,000 litres[120].

4.4 MOVING TO PLASMA SELF-SUFFICIENCY: IMPACT ON WHOLE BLOOD SUPPLY

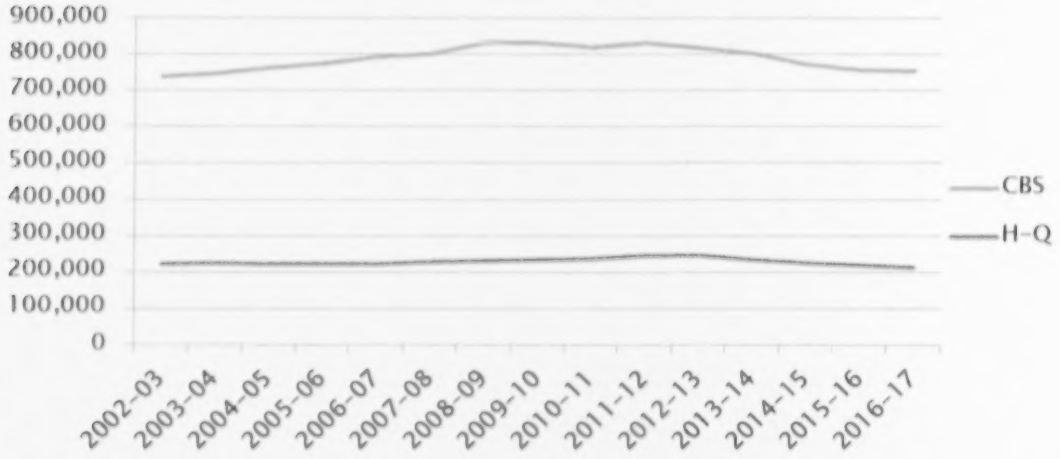
One of the issues the Panel was asked to comment on was the risk to the whole blood supply of pursuing plasma self-sufficiency with the expansion in Canada of source plasma collection. This has been a concern raised by blood operators both in Canada and other jurisdictions and this concern is further elevated when source plasma donors are paid.

The amount of whole blood collected by a blood operator is driven by the clinical demand for red cells. Clinical and surgical innovation and evidence-based blood management practices have evolved significantly over the last 2 decades, significantly reducing the demand for red cell transfusions. This has resulted in a decline in the demand for whole blood collection in Canada, the US[121,122], Europe[123] and elsewhere[124]. Figure 4.3 illustrates the demand curves for CBS and H-Q over the last 14 years. Over the years where red blood cell collections were falling in Canada, neither CBS or H-Q had any significant source plasma collection activity – thus this trend truly reflects the falling requirements for whole blood.

The US, which historically remained a high user of red cells compared to other jurisdictions, experienced a 25% decrease in red cell transfusions between 2008 and 2015[121].This is an important trend which some stakeholders confound with the impact of source plasma collection, but the literature is clear that it is a trend which relates to reduced clinical demand and not the inability to collect sufficient voluntary donors of whole blood.

Overall blood collection organizations in the US and Canada continue to consistently meet the needs of hospitals for blood, with normal cyclical shortages which are largely seasonal, or shortages of specific products such as O-negative red cells associated with poor adherence to best practice blood management of this important product[125]. Over time, it would be worthwhile to monitor the potential impact of source plasma collection on these products and on the recruitment of apheresis platelet donors.

Figure 4.3: Number of Red Blood Cell Shipments



Data from CBS, 2017; H-Q, 2017

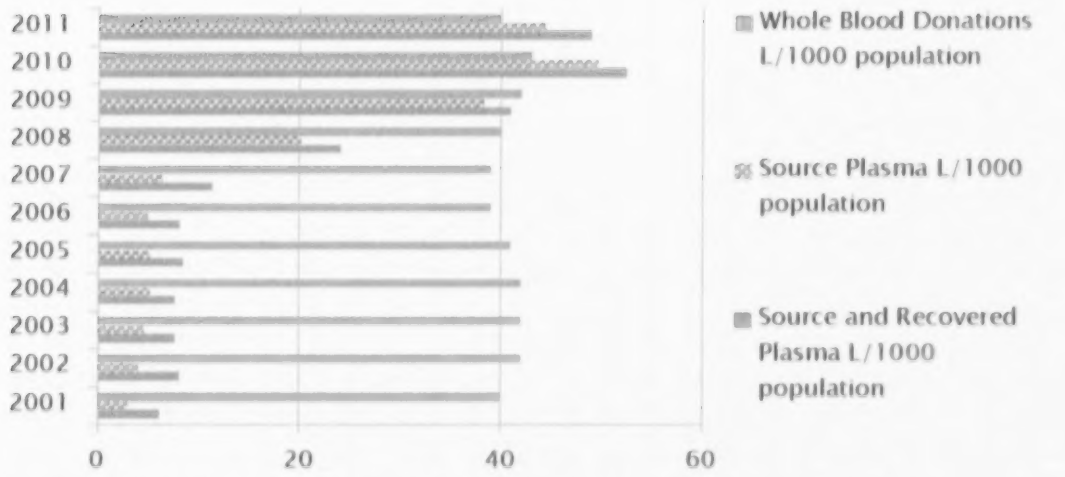
The US is the jurisdiction with the longest history of commercial plasma collection and greatest risk of a negative impact on the whole blood supply from competition with commercial plasma collection. As the US plasma collection system continues to grow in response to ongoing global demand for plasma collection it is possible that US non-profit blood operators may face increased challenges in donor recruitment and retention. However at this time, these operators are more concerned with the declining **demand** for whole blood which has significantly decreased revenues as well as raised challenges to donor engagement. As a way to both retain donor engagement and diversify revenue streams, some US blood collection centres have initiated volunteer source plasma collection programs, either within their blood centres or at separate plasma collection sites. Whole blood donors who have been deferred from donation, or who have a blood type that is in less demand, may be targeted for conversion to plasma donation[126]. To date these non-profit source plasma collection programs are small and just in development.

Hungary is one of a small number of EU states which allows compensation of donors and has experienced an expansion of commercial plasma collection. Some stakeholders have suggested that this has affected the Hungarian public blood operator's ability to meet hospital demand for blood. In a European Commission report Hungary reported having experienced less blood shortage in 2014 than in prior years and was 1 of only 3 EU Member States that did not report having taken measures such as information campaigns or donor events to promote voluntary donation of blood and blood components[107]. The Hungarian Blood Transfusion Service has confirmed directly to the Panel that they have monitored whether the private plasma centres were impacting whole blood collection. They have found no significant reduction in their blood donor population, or data that demonstrate an impact of private plasma collection on whole blood collection. While there has been a decrease in whole blood

donations, they believe that is tied to other factors. They are not in blood shortage: hospitals' blood needs continue to be met.

A review of data from the Czech Republic both before and after a 2007 law allowed source plasma donors to receive monetary compensation indicates that the overall plasma collection volumes increased without a significant impact on whole blood donations[127](Figure 4.4). Other reports have shown a positive correlation between whole blood units per capita and litres of plasma for fractionation per capita in European countries[128,129].

Figure 4.4: Temporal trends for Czech Republic Before and After 2007 Legislative Change



Data from Janssen, M. P., L. R. van Hoeven, and G. Rautmann. 2015. Trends and Observations on the Collection, Testing and Use of Blood and Blood Components in Europe: 2001–2011 Report. Strasbourg: European Directorate for the Quality of Medicines and HealthCare, Council of Europe.

Other reports have used examples from Austria and Germany to demonstrate that a private paid donor system has caused shortages of whole blood in the past. It is important to note that the example repeatedly cited relates to a specific non-profit blood collector facing competition from a private *blood* collector to supply hospitals with blood components for transfusion, *not* competition from plasma collection centres. The private blood collector withdrew their operations at short notice thus risking interruption of its hospital customers' supply of fresh blood components[130,131]. In a formal 2014

European Commission survey, neither Austria nor Germany reported regular blood shortages[105]. In fact, Germany reported a surplus of platelets, plasma and red blood cells[107].

In Canada, after the initiation of its Plasmavie centres H-Q observed localized drops in whole blood donations, which were managed by adjusting the intensity of mobile collections in other regions. H-Q reports no impact on its capacity to meet hospital demands and inventory levels remain high and stable. Almost all (98%) of its hospital customers were satisfied with H-Q's products and services in 2016-17[57]. A decrease of whole blood donor registrations over the period 2015-2017 was more than made up for by new plasma donor registrations, resulting in a net increase in collections overall[96]. H-Q blood collection operations are largely achieved through mobile units (85% of total collections)[132] thus providing high flexibility about the place and volume of collections, another strategic advantage to mitigate local impacts.

In 3 cities served by CBS, private sector companies also collect source plasma. Available evidence on whether plasma collection operations have affected CBS operations is as follows:

- Winnipeg (1 site, open for >30 years): Prometic currently operates a 24-bed commercial source plasma collection facility; CBS has not indicated that those activities have affected CBS operations or are of concern;
- Saskatoon (1 site, open since Feb 2016): CPR currently operates a commercial sources plasma collection facility with a targeted capacity of 40,000L per year (current data indicate this site is well below targeted collections); CBS indicated it saw a decline in new 17 to 25-year-old donors in the months following the opening of the CPR site however the CBS blood centre also relocated during that period. CBS also noted anecdotal reports of CBS/CPR brand confusion for donors. In its October 2017 oral presentation to the Panel, CBS indicated that there was no significant trend that CPR operations were affecting CBS Saskatoon operations, where its collections are still increasing year over year;
- Moncton (1 site, open since July 2017): CPR currently operates a new site with a targeted capacity of 40,000L per year. Given the short timeframe there were insufficient data available.

According to CBS corporate reports, it met or exceeded its percentage target rates for filling hospital red cell and component orders in 2016/17 and the first half of 2017/18[133]. In 2016–2017, CBS increased its overall blood collections by approximately 5 per cent over the previous year, over half of which was collected from new or reinstated (lapsed for > 12 months) donors.

In summary, the Panel found that the impact of source plasma collection on the whole blood supply, although a critical issue, was poorly researched. To date, there was no clear evidence that unpaid or paid source plasma collection is having a negative impact on the blood supply. However, there needs to be more work done to track this over time.

CHAPTER 5

KEY STAKEHOLDER PERSPECTIVES

As noted throughout the document, the Panel solicited the perspectives of key players who have a stake in issues related to the safety and security of supply of IG and other PDPs. Stakeholders were invited to submit their perspectives relevant to the Panel's mandate in writing and many also participated in roundtable discussions with the Panel by phone or in person. The Panel greatly appreciated and relied on their input in this report, though not directly attributed to them. See Appendices D-G for further detail, as noted below.

5.1 CANADIAN STAKEHOLDERS

5.1.1 PATIENT GROUPS

Eleven patient organizations that represent key groups that rely on PDPs were invited to submit written input on issues relevant to the Panel (see Appendix D). Six organizations responded: Alpha-1 Canada; Canadian Hemophilia Society; Canadian Immunodeficiencies Patient Organization; Hereditary Angioedema Canada; Immunodeficiency Canada; and Network of Rare Blood Disorder Organizations. Note that while some of these represent individuals with a range of disorders, there is no Canadian umbrella group comparable to Platform of Plasma Protein Users (PLUS) or American Plasma Users Coalition (A-PLUS) discussed in Section 5.2.2.

The Canadian patient groups raised a number of issues for the Panel to consider. Four of the 6 patient groups anticipate a rise in the diagnosis and treatment of rare disorders. These groups note that many Canadians remain undiagnosed and this will change over the coming years with a rise in prenatal screening and increased disease awareness.

While voluntary plasma donation in Canada is encouraged by all the patient groups who responded, they also recognize that the global plasma supply will continue to depend on commercial plasma centres using paid donors, and call for cooperation and collaboration between the 2 sectors. Five of the 6 patient groups explicitly stated their support for paid plasma in order to ensure sustainability of supply of vital PDPs for patients and seemed to share the view expressed by Canadian Immunodeficiencies Patient Organization that "Canadian patients would rather receive Canadian plasma from compensated Canadian donors than US plasma from compensated US donors."

Some patient groups that use PDPs other than IG raised issues of inequitable access and affordability across PT jurisdictions. These groups advocated for mechanisms to be in place to assure continued access and funding to ensure treatment with the required PDPs remains available and affordable for patients.

5.1.2 PHYSICIANS AND OTHER HEALTH CARE PROVIDERS

The Panel spoke with several expert physicians (see Appendix C) in the IG field as well as members of the NAC on Blood and Blood Products (see Appendix C for list of members). Additionally, thirty organizations (see Appendix E) representing health care providers were invited to provide input to the Panel via written brief and/or by participating in a roundtable discussion with Panel members. Three organizations responded: the Canadian Rheumatology Association (CRA), the Canadian Society of Allergy and Clinical Immunology (CSACI), and the Ontario Regional Blood Coordinating Network (ORBCoN). This section highlights some key points expressed that reflect perspectives heard from these individuals and organizations.

A primary concern of clinicians is the need to ensure ongoing safety and availability of IG and other PDPs, very much in alignment with the views of patient groups.

They would also like patient and health care system impact issues to be better taken into account in product purchasing decisions. For example, there is a strong patient and clinical trend favouring SCIG over IVIG, where feasible and appropriate for the patient. SCIG allows patients to administer their own medication in the community and provides significant convenience as well as cost savings to the health system. Adverse reactions were also flagged to be less common with SCIG (IVIG headaches are a significant issue). There may be further opportunity to reduce IG usage with clearer SCIG therapeutic dose ratios. A 2012 Canadian economic analysis estimated that home-based SCIG treatment reduced healthcare system cost by > $5,000 per patient over 3 years compared to hospital-based IVIG[134]. A recent decision to reduce the number of suppliers for some SCIG products also limits brand choices that help avoid adverse reactions in some patients. It was felt that these advantages of SCIG are not reflected in recent product line decisions. Participant organizations are not included in the product line decision-making process of CBS.

Specialists prescribing IG also commented on the need to improve prescribing practices so that clinical guidelines are followed to reduce the amount of IG over-prescribing, e.g. use of IG for ITP as front-line therapy, which is not aligned with national guidelines. They also raised the fact that PDPs as a drug remain cost-free and this does influence treatment decisions. Some health care providers would welcome a national approach to IG guidelines, and electronic IG access control systems.

The NAC and many clinicians charged with the "gate-keeper" role on the issuing of IG shared their frustration about the relative ineffectiveness of the UM function in their jurisdictions. They indicated that, although most IG use was aligned with appropriate indications, there was still room for improved utilization of IG through a more effective process that would borrow from other jurisdictions and include more robust guidelines, evidence-based dosing protocols, and more attention to the criteria for ongoing treatment.

5.1.3 OTHER CANADIAN HEALTH STAKEHOLDER GROUPS AND UNIONS

Eleven Canadian unions and organizations that advocate for public health care were invited to submit written input on issues relevant to the Panel (see Appendix F). Seven organizations responded: Canadian Health Coalition; Blood Watch; Council of Canadians; the New Brunswick Health Coalition; Canadian Labour Congress; Canadian Federation of Nurses Union; and the Canadian Union of Public Employees (CUPE).

The respondent groups all object to for-profit plasma collection in Canada, for reasons including the following:

- Paying plasma donors contravenes the Krever report recommendations in favour of voluntary donor models;
- Concerns related to the safety of PDPs made from plasma from paid donors;
- Concern that commercial plasma centres represent a move towards privatization of the public health system;
- Moral/ethical opposition to paying for blood or plasma due to the perception that it negates the benefits of a solely voluntary-based donation system, and that it targets vulnerable populations.

These organizations declared their support for the CBS initiative to collect more plasma by opening 40 new voluntary donor plasma collection sites. They also called on the Government of Canada to halt licensure of paid plasma businesses in Canada, including CPR.

In contrast to the other groups above, a group of >30 ethicists and economists submitted an open letter to the Panel expressing concerns about banning compensation for plasma donors and the resulting impact on the ability to secure a sustained and safe supply of IG for patients in Canada. This open letter also addressed key points frequently raised in the debate, including: wrongful exploitation, commodification, altruism, safety and security. Approximately half of the signatories were Canadian, while most of the rest were from the US (Appendix G).

5.1.4 CANADIAN BLOOD OPERATORS

Senior staff with CBS and H-Q met with the Panel and discussed IG self-sufficiency and the various aspects of their role and strategies in securing the supply of IG and other PDPs for Canada. They provided extensive data and input requested by the Panel, which contributed greatly to the evidence base and the Panel's work. Both operators described their strategic activities over the years to ensure an adequate supply of PDPs and expressed their commitment to reducing Canada's reliance on US plasma collection. Both organizations were clear in their confidence in the safety of the products which are in

use but have established plans to increase source plasma collection in Canada with a goal of greater self-sufficiency.

CBS discussed its business plan for expanding source plasma collection across Canada (up to 40 sites spread across the country) and shared its views on the potential impact of commercial plasma collection activities on the blood supply in general.

5.1.5 FRACTIONATORS

The Panel invited input and heard from several fractionators, some of whom are under contract with CBOs (CSL Behring, Grifols) for both toll fractionation of Canadian plasma into some PDPs and the supply of others made from commercial plasma to meet the needs of Canadians. The Panel also heard from senior representatives from 3 fractionators located in Canada: Green Cross (Montreal), Evolve Biologics (Toronto), and Prometic (Winnipeg). Fractionators provided insight into their business models, their approaches to source plasma collection, fractionation capacity in the US and globally, emerging innovations for maximizing extraction of therapeutic proteins from plasma, and the safety framework for IG and PDPs. All stated that they welcomed any opportunity to work with both CBOs and Canadian regulators.

5.1.6 PLASMA COLLECTORS

The Panel invited input and heard from Canadian commercial plasma collectors as well.

Canadian Plasma Resources (CPR) is licensed to collect plasma from paid donors in 2 collection centres in Canada, located in Saskatoon, Saskatchewan and Moncton, New Brunswick. It stated to the Panel its interest in working with federal and provincial governments and Canada's blood operators to help increase the supply of plasma in the country.

Prometic Life Sciences Inc. operates 1 commercial plasma donation centre in Canada in Winnipeg Manitoba and is also a biopharmaceutical manufacturer.

5.1.7 PUBLIC OPINION SURVEYS

While the Panel did not conduct public opinion research, it reviewed findings from 2 public opinion surveys.

In June 2016, Ipsos Reid conducted a public survey for CBS on the issue of pay-for-plasma. Reported results indicated that[135]:

- 76% believe paying for plasma donations will lead to fewer people being willing to donate blood to CBS on a voluntary basis;
- 57% of Canadians believe paying people for plasma is a step in the right direction, while they largely agree (81%) that CBS should not pay plasma donors.

Ipsos Reid drew some conclusions from these survey results, including the following:

- "Canadians appear willing to accept both the public collection of plasma by [CBS], as well as private sector, for-profit collection. However, [CBS] should not be involved in for-payment collections."
- "Plasma remaining in Canada, accountability, and safety are primary concerns which encourage support for [CBS]' decision NOT to pay for plasma. However, support for private sector plans improves if economic benefits can be realized."

In October 2017, Professors Mario Macis (Johns Hopkins) and Nicola Lacetera (University of Toronto), both economists who have published in the area of prosocial behavior and the intersection of ethics and economics, surveyed Canadians and Australians to measure their moral/ethical concerns related to compensation for plasma donations. Of the 826 Canadian respondents, >70% approved of paying plasma donors as being morally appropriate, contributing to domestic supply, and in recognition that they were already being paid elsewhere. Approximately 50% of those initially opposed to paying donors would consider payments acceptable if domestic supply and imports were insufficient[136].

5.2 INTERNATIONAL STAKEHOLDERS

5.2.1: PUBLIC POLICY ORGANIZATIONS

The WHO is the directing and coordinating authority on international health within the United Nations' system, and leads a number of initiatives to support both blood transfusion safety as well as PDPs and other biologicals. For example, the WHO supports the international Blood Regulators Network (BRN) to facilitate knowledge exchange among government regulators of blood and PDPs. The WHO has consistently stated that governments should achieve a self-sufficient and sustainable national blood supply by committing to voluntary, non-remunerated, blood donations. Highlights from a few key policy documents from other international bodies are reviewed in Chapter 4.

The European Directorate for the Quality of Medicines and Healthcare enables and supports the development, implementation, and monitoring of quality standards for safe medicines and their safe use, including guidance and standards in the areas of blood transfusion, founded on a principle of voluntary and non-remunerated donation[137].

5.2.2 COALITIONS OF PATIENT GROUPS

The American Plasma Users Coalition (A-PLUS) is a coalition of US national patient organizations created to address the unique needs of patients with rare diseases that use life-saving plasma protein therapies. A-PLUS advocates on behalf of these patients' interests, for example by developing and filing formal recommendations with the US FDA in response to stakeholder consultation opportunities[138]. Its

European counterpart is PLUS, a consortium of 7 patient organizations representing people living with disorders treatable by PDPs. Each of these coalitions speaks for >100,000 individual patients[103]. Shortly after the opening of the CPR plasma centre in Saskatoon, PLUS and A-PLUS signed a joint letter to state that paid plasma was safe and not unethical, and that both private and public sector plasma collections are needed and should be permitted to co-exist as has been done in several countries without detriment to the blood supply[139].

Notably, PLUS initiated and continues to organize a recurring Dublin conference that has resulted in an evolving series of Dublin Consensus Statements on the supply of PDPs (2010[140], 2011[110], 2012[66]). These conferences engaged a wide range of stakeholders, including patient groups, blood donor associations, for-profit and not-for-profit blood collectors and PDP manufacturers. The most recent formal Statement was in 2012, which reiterated that an insufficient supply of PDPs is a major safety risk to patients and recognized that both private and public sectors are needed to meet global demand for PDPs.

5.2.3 BLOOD OPERATORS AND ASSOCIATIONS

The International Society of Blood Transfusion (ISBT) is a scientific society formed to share knowledge among transfusion medicine professionals to improve the safety of blood transfusion worldwide. A number of ISBT Working Parties focus on the study of specific topics. ISBT publishes the Vox Sanguinis journal.

The American Association of Blood Banks leads standards development, accreditation and implementation of quality systems in transfusion medicine and cellular therapies. It focuses on donor and patient safety through knowledge translation and convening learning events[141].

The European Blood Alliance (EBA) is an association of 26 European not for profit blood establishments collaborating to improve the availability, quality, safety and cost-effectiveness of the blood and tissue supply in Europe and to raise awareness of voluntary and non-remunerated donation of blood and blood components. A 2016 EBA statement expressed concern that commercial paid donor operations were eroding the nonprofit blood donor base. No details or evidence was provided, but the concern was expressed in the context of competition between public and private blood collectors for hospital clients. The statement also expresses concern about the low efficiency ratios of plasmapheresis collection in non-profit blood establishments. The EBA recommended that blood, including plasma, be considered a strategic resource[142].

The Alliance of Blood Operators is a closed network of not-for-profit blood operators with voluntary non-remunerated blood donor bases. Its members collaborate to drive member performance improvement, knowledge exchange, and resolution of strategic issues for the benefit of patients and health systems[143].

Approximately 1/4 of the 190 members of the International Federation of Red Cross and Red Crescent Societies are responsible for blood service delivery in their national blood programmes. The International Federation of Red Cross and Red Crescent Societies formally supports and advocates the principle of voluntary non-remunerated blood donation, and supports the goal of national self-

sufficiency, including ensuring adequate supply of blood and blood products to meet domestic health needs[144].

In Australia, the NBA is the body that implements the collective decisions of the federal, state and territorial governments regarding the budget and targets for the operation of its sole blood and plasma collector, the Australian Red Cross Blood Service. As mentioned in Chapter 4, the NBA has a managed growth approach to plasma collection and has launched a new program of IG UM which will limit access to IG unless the patient's case has been documented to meet the criteria[145,146].

5.2.4 FRACTIONATION ASSOCIATIONS

The International Plasma Fractionation Association (IPFA), which is the association of state and non-profit fractionators, supports organizations and countries that work to provide a safe and secure supply of blood and PDPs based on the principles of 'not for profit' and the voluntary non remunerated blood donor. It promotes the interests and activities of its member organizations involved in the collection of human blood and plasma and the manufacture and supply of PDPs. Its main priority is to maximize the availability of recovered plasma[147]. The IPFA considers plasma to be a strategic resource, i.e. an economically important raw material subject to a risk of supply interruption, for which countries should strive for strategic independence, i.e. seek to safeguard the national or regional supply, involve government authorities, and cooperate among stakeholders[148].

The PPTA represents private sector manufacturers of PDPs and recombinant products. It argues that a safe and secure supply of plasma products requires the co-existence of both paid donor and non-remunerated donor systems and the active collaboration of the 2 systems. It establishes safety and quality standards for the manufacturing of PDPs. PPTA suggests a range of strategies to increase plasma, including collecting more outside the US, allowing public and private centres to compete in Europe, and increasing efficiency in collection practices[149].

Both PPTA and IPFA recommend that countries increase their plasma collection.

CHAPTER 6

CONCLUSION

For many decades, PDPs have been critical products for patients in Canada and globally. Since the introduction of recombinant F VIII, IG has been and continues to be the leading PDP product utilized in Canada and globally. The demand for IG continues to grow driving the need to collect more plasma for the manufacture of both IG and all other plasma-derived products.

In this section of the report, we lay out the logic behind our thoughts and conclusions in regard to our mandate. Our conclusions are grounded in the extensive evidence base established in preceding chapters. The information in the preceding chapters is heavily referenced and the Panel has not reiterated these references in the Conclusion.

Canada is 100% self-sufficient related to the supply of whole blood and fresh components, all of which come from voluntary blood donations through the programs operated by Canadian Blood Services and Héma-Québec. However, as noted in the preceding chapters, most of the supply of IG and other PDPs used in Canada is purchased from US commercial manufacturers. The demand continues to grow in the range of 6-8% per year.

Demand for IG

There is no indication that the pattern of growth in demand for IG will dramatically change within the next ten years:

- There is no substitute product which could replace IG and significantly diminish demand for the plasma-derived product currently in use;
- There appears to be no looming indication for the use of IG in a high prevalence illness (such as established Alzheimer's disease) which would significantly increase demand and change the demand curve from linear to exponential, thus creating potential shortages.

The Panel was convinced from the review of the literature, examination of best practice in other jurisdictions and discussions with Canadian experts that more could be done to mitigate inappropriate use of IG and other PDPs. This will also contribute to self-sufficiency goals as well as ensuring a secure supply of product to meet real need. Related to this the Panel urges that a number of initiatives be considered by PT governments who bear the burden of managing this issue:

- National Guidelines for IG use (and other PDPs) need to be developed through a structured process – currently guidelines differ across the country and there appears to be no clinical rationale as to why this should be the case;
    - The UK and Australia have robust guidelines and every advantage should be taken to not reinvent the wheel in Canada;
    - CADTH could be tapped to review any new PDPs using a process similar to what they use for other new drugs being considered by FPT drug plans – this would bring the review of PDPs to the same standard as other drugs. The CBOs are an efficient procurement platform for PDPs given the complexity of the supply chain of PDPs but their capacity for robust review does not meet the standard of CADTH (or INESSS in Québec).
- There is a strong need for a much enhanced and universal gate-keeper function for the release of IG (as well as other PDPs) across all PT jurisdictions;
    - The NHS currently has the most robust structure for this kind of decision-making and their utilization statistics reflect this – many jurisdictions including Australia (which has a constitutional structure comparable to Canada) are working to tighten their processes in this area.

Security of IG Supply

There appears to be no emergency or crisis related to supply of IG for Canadians:

- The data show fairly consistent linear growth of both demand and supply for IG: supply is keeping pace and is expected to continue to do so through the medium term. There is capacity for expansion in both fractionation and plasma collection operations globally;
    - Although there is talk of overall saturation of the US plasma collection market the Panel found no evidence of this;
    - There was some evidence of saturation in very local markets within the US where numerous companies were competing with each other to attract plasma donors, resulting in higher rates of compensation for donors and aggressive branding and marketing campaigns.
- The price of IG on the market has increased but at a much lower rate than the increase in demand, thus affordability constraints due to price increases are not apparent in the short and medium term.

PDP Supply Interruption

While there are no urgent concerns about the overall security of the IG supply as noted above, the possibility of acute shortages exists. Certain acute hazards can and have risked interruption of the supply of IG and PDPs over the past few decades, and could recur:

- Emerging infectious agents such as vCJD in the UK that caused an acute crisis in the supply of plasma for its state fractionator (Bio Products Laboratory) with resulting constraints on the supply of IG for UK patients. The Zika virus was a potential threat to global plasma supplies – however rapid and co-ordinated action by scientists, fractionators, blood operators, and regulators clarified the risk and the associated risk management strategy and there were no significant shortages experienced;

- There have been occurrences of production shut-downs in individual fractionation facilities resulting in shortages in product supply by these fractionators. Generally clients are able to access replacement products through other suppliers.

The risks of acute shortages in the future are likely to stem from similar dynamics as noted above. Other risks are more remote:

- There is a remote risk of a US Executive Order (for National Defense Resources Preparedness) or a collapse in a US/Canada trade agreement compromising supply of IG or other PDPs but it is very difficult to predict;

- A new indication for IG treatment which impacts large numbers of patients (the anticipated use of IG for patients with established Alzheimer's disease was an example of such a risk) could significantly increase demand but there would be evidence growing over a number of years as the results of clinical trials became known.

Strategies to risk manage acute and more prolonged shortages are essential to have in place in Canada:

- Over the last 15 years, both CBS and H-Q have put in place best practice strategic procurement processes to protect against dependency on one supplier of IG and other PDPs and mitigate the risk of local production problems which could cause an acute shortage – these strategies should continue;

- There does need to be a national prioritized list of patient groups dependent on IG which will allow appropriate allocation of the product in the setting of an acute or prolonged shortage – this has not been done in Canada.

    - Such an approach would need sign off by all PT governments and could perhaps utilize the expertise and authority of their Chief Medical Officers of Health who have legislated responsibility in the event of public health emergencies.

Plasma Supply – International

There is growing international concern about the high global dependency on the US for the collection of source plasma (US collects 74% of global source plasma used in the manufacture of PDPs.) This concern is compounded by the fact that the majority of US plasma comes from paid donors.

- The Panel notes that the vast majority of jurisdictions, including the majority of member states in the EU, UK, and Australia, still rely heavily on US plasma to meet their needs for IG and other PDPs. The only countries self-sufficient in PDPs are those that allow compensation of their source plasma donors;
- There is a growing acceptance across jurisdictions that self-sufficiency strategies should be designed to avoid being totally dependent on any one country for PDPs, and instead achieve a balance between dependency on the commercial market, and the incremental cost of collecting source plasma from local volunteer donors.
    - The approach taken in Australia weighs the cost and feasibility issues of local volunteer source plasma collection against the benefits of a higher level of self-sufficiency. On a regular basis, plasma collection targets and related budgets are set by the National Blood Authority; the rest of the needs of Australians are met through competitive procurement of PDPs off the commercial market.

Safety of PDPs

The Panel reaffirms the safety of PDPs made from paid donor plasma under the current strict regulatory regimes (in Canada, USA, EU and other jurisdictions) a position articulated by regulators, blood operators, and patient groups around the world.

- There has been no proven transmission of infection via PDPs over the last 20 years, a fact that is attributable to the multi-pronged approach to ensuring safety of PDPs outlined in Chapter 4. Our review of the history of vCJD in the UK failed to identify compelling proof of infection of patients through PDPs;
- As compared to whole blood, plasma for PDPs is subjected to a number of steps incremental to the current screening and testing applied to whole blood donations, including: 60 day hold, NAT testing of plasma pools, and stepwise viral/pathogen inactivation;
- The fractionation sector through its Associations provides rigorous quality programs which further enhance safety of PDPs. These voluntary standards could be mandated in regulation or at the time of procurement by Canada;
- A thorough review of available laboratory screening results and residual risk calculations show clearly that there is no difference in the risk profile between qualified paid source plasma donors and whole blood donors.

The ongoing challenge of emerging infectious threats to the blood supply will continue into the future, particularly with global warming and the growing complexity of global migration patterns. Canada could draw from international examples to consider enhancing its systems to mitigate future emerging infectious threats:

- While surveillance and early warning systems about threats to the blood supply have been put in place since the Krever report, there is a need for a more structured and coherent approach:
  - Currently, much of the activity depends on various data sets and the voluntary sharing of data by Provinces and Territories resulting in time lags in reporting and a lack of consistency and comprehensiveness;
  - One committee which has the exclusive mandate to acquire comprehensive data on a regular and timely basis and provide the appropriate, regular analysis and advice to Health Canada or Provinces and Territories in regard to evolving threats could be put in place to assure a systematic and regular approach to enhance this activity;
  - Current oversight systems have not foreseen that multiple players would be involved in plasma collection, so consideration should be given to consolidating critical information in one place - such as one donor deferral registry for Canada.

Plasma Collection in Canada

The question of whether Canada should increase its self-sufficiency in plasma collection and to what degree was discussed at length by the Panel.

- The Panel clearly agrees that Canada needs to make a much more significant contribution to the collection of source plasma – the Plasmavie program and the desire of CBS to increase collection of source plasma from their donors are an appropriate response to the significant dependency on the US as a source of plasma;
- It is appropriate for Canada *at a minimum* to be able to provide sufficient plasma to meet the needs of the one group who are truly life dependent on IG – those patients with primary immunodeficiency (PID). This would ensure that these patients are protected in the unlikely event of a severe shortage. Volume targets beyond this minimal expectation should be aligned with priority clinical needs;

- The move to collect more source plasma by CBOs needs to be based on solid business principles and learnings and/or partnerships with the private sector that have significant expertise. Increased source plasma collection by CBOs cannot be undertaken at *any* cost.
    - There is a significant premium related to the cost of collecting high volumes of plasma from volunteer source plasma donors; this was acknowledged by CBS and was reaffirmed by discussions with other jurisdictions;
    - There are also feasibility challenges to actually meeting collection targets for source plasma from volunteer donors; this has been acknowledged by many non-profit operators who are trying to expand source plasma collection from volunteer donors;
    - The CBS plan is based on source plasma collection from volunteer donors over 40 collection centres spread across the country. This approach will be limited by a high cost structure:
        - CBS has indicated in the last few weeks that they are considering a more consolidated approach and this should be encouraged - note that Australia is currently piloting larger plasma-only collection centres;
        - The self-sufficiency goal of CBS may overestimate demand based on their expressed rationale.
- The UK patient prioritization scheme is considered best practice and could be re-examined as a more robust framework for determining the amount of plasma needed to meet the needs of patients exclusively dependent on IG.

The Panel recognizes that CBOs have pursued many of the activities embedded in the concept of **strategic independence** over the last 2 decades (multiple strategies including strategic procurement, collection of local plasma, supply guarantees, the use of toll fractionation and the concept of regional self-sufficiency).

- This approach should continue and be further enabled by enhanced source plasma collection in Canada.

As noted, there are a number of provinces in which commercial plasma operations are currently permitted. The Panel agreed that creative options should be carefully examined to ensure that all source plasma collected in Canada from Canadian donors (whether paid or volunteer) be made available for the needs of Canadian patients. This would enhance Canada's self-sufficiency.

- Legislative and regulatory options to achieve this might include:
    - conditions for licensing of commercial plasma centres;
    - a first right of refusal for CBOs to purchase Canadian private sector plasma or Canadian sourced PDPs from commercial operators on reasonable business terms;

- limitations on export of Canadian plasma without a plan to return products for the use of Canadians on reasonable business terms.

Grandfathering of current private sector operations and the application of any changes to future entrants could mitigate the risk of this approach.

Fractionation Capacity in Canada

The Panel recognized a small but emerging fractionation industry in Canada, recently significantly expanded by the opening of the Green Cross facility in Montreal, Québec.

- Some of the small producers are using innovative technology which could significantly increase the yield of protein products from a litre of plasma – something which can also contribute to a higher level of self-sufficiency;
- The Panel encourages CBOs and all governments to encourage and enable innovation which will help attain an appropriate level of self-sufficiency through increased productivity in the production process.

Use of Donor Incentives

The issue of volunteer versus paid donors in the drive to achieve local self-sufficiency targets remains contentious and internationally there is no consensus.

The rationale for self-sufficiency based on **volunteer** donors of plasma is generally grounded in:

- The ethical, legal and social implications of paid transactions involving human bodies and bodily material in medical treatment and research;
- The history of the contamination of the global blood supply with HIV and Hepatitis C in the 1970s and 80s with tragic results and ongoing concern from some stakeholders in regard to the safety of paid donations;
- Additional concerns from some stakeholders that there is insufficient attention paid to the health of paid (commercial) source plasma donors who tend to donate much more frequently than volunteer donors.

After examining the available facts, the Panel felt that key trends are important to recognize:

- The continuum between the "paid" commercial plasma donors and "volunteer" plasma donors has changed significantly over the last 2 decades – the evidence shows a wide array of

incentives are used across jurisdictions to attract "volunteer" donors – thus the definition of a volunteer donor is certainly changing and needs to reflect this reality;

- In Canada, the compensation currently offered to CPR commercial donors is within the range of incentives paid to EU donors for volunteer donations;
- In Canada, specifically Manitoba, source plasma donors (these are no longer just women with anti-D) have been paid for many years – first by the Rh Institute and currently by the commercial operator Prometic;
- A good example of the changing norms is the recent decision by Sanquin (Netherlands blood operator), one of the longstanding national blood operators operating under a legislated self-sufficiency mandate, to move to increase its incentives for donors in response to challenges in meeting collection targets.

+ Much of the cost-efficiency of the commercial source plasma sector stems from the very significant commitment of their qualified paid source plasma donors; expecting this kind of commitment from volunteer donors is unrealistic based on experience to date and this speaks to the feasibility challenge of meeting aggressive source plasma collection targets using the volunteer donor sector.
  - The legislative framework covering a significant percentage of donors in the country (Alberta and Ontario) precludes paid donation other than on an exceptional basis by CBS – it may be necessary for CBS to exercise this option at some point to enhance source plasma donation. (Québec legislation does not allow Héma-Québec that option.) Consideration should be given to strengthening the regulatory framework in regard to the health of qualified source plasma donors in Canada.
+ The question of safety of IG and other PDPS made from paid plasma donors is moot – there is no increased risk of paid plasma donors under current regulatory frameworks; the other ethical, legal and social considerations in regard to compensated donors are real and remain an issue for policy makers, donors and stakeholders.

Access for Patients to Other PDPs

The Panel was also concerned with the existing inequities in regard to access to specific PDPs for some groups of patients across different jurisdictions. This was an issue which the Panel felt was outside their mandate but merited further work and consideration:

+ The review of all new PDPs entering the marketplace by CADTH would help with this issue by ensuring clear decisions in regard to effectiveness and the appropriate clinical indications;
+ In Canada, the longstanding principle that plasma-derived products should be provided to patients at no cost along with all other blood and component products is something which should be discussed by all PTs and the federal government together.

- Given donors across the country contribute their plasma for these products now and potentially will do so to a greater degree in the future, clarification of this longstanding principle and the development of a transparent approach across the country to this equity of access issue would be helpful;
- This outcome of these discussions could provide clarity to patient groups and some clinicians who worry that there would be a move to place PDPs on provincial drug plans which would increase the cost for many patients due to co-pays.

Impact of Plasma Collection on the Blood Supply

The issue of whether expanded source plasma collection as part of a national self-sufficiency policy could negatively impact the volunteer blood supply was an important topic considered by the Panel. Based on extensive discussion and an examination of the available evidence, the Panel concluded that there was no evidence to suggest this was a current issue, however, ongoing oversight and tracking of the issue is critical and further research is necessary:

- Some local evidence in a small number of EU jurisdictions suggested that expanded plasma collection had a positive impact on whole blood donations;
- There is conflicting evidence in regard to whether commercial plasma collectors and non-profit blood operators target the same donors;
  - In Canada, CBOs use mobile clinics to collect much of their blood, and generally the demographics of their donors are different from those of commercial plasma centres.
- The range of compensation available for frequent qualified paid plasma donors suggests this could have an impact on volunteer whole blood donors. Though no hard data were found, the issue has not been rigorously studied to date;
  - In Canada the compensation of commercial donors does not appear to be impacting whole blood donors to date;
- There was evidence that the private plasma collection sector had significantly changed their marketing and branding over the last few years, shifting to an approach much more aligned with traditional blood operators and in some cases resulting in confusion on the part of donors.
  - Nuancing of Health Canada licensing conditions on commercial plasma collection centres could address this risk.

Closing

In summary, much has changed since the release of the Krever Commission report in 1997. PDPs are safe, the plasma sector has been able to respond and react to continuing changes in demand over the last 20 years ensuring care for patients in Canada. New products continue to be developed to address serious health conditions. CBOs use sophisticated strategies with the support of provincial, territorial and federal governments to ensure the sustained supply of safe and affordable products for patients in Canada. However, like most of the world, Canada is too dependent on one jurisdiction (US) for the supply of the vital raw material used to make these products. Canada needs to do more to collect plasma and take other steps to enhance its self-sufficiency in meeting the needs of our citizens for PDPs. As discussed there are a number of decisions to be made and strategies to be considered. In the implementation of the strategies, there needs to be transparency for the public and stakeholders, adherence to good business principles with appropriate flexibility in the approach, due consideration of the taxpayer, and ongoing attention to the outcomes with the capacity to adjust where necessary. The Panel has consolidated much of the evidence available related to these issues in this report and we respectfully submit it to the Deputy Minister of Health Canada in the hopes that it will enable a robust discussion across the country on the way forward in a critical area of public health care in Canada.

GLOSSARY OF TERMS

Apheresis: A procedure where whole blood is removed from the body and a desired component is retained, while the remainder of the blood is returned to the donor. Apheresis procedures may be done to collect donations or to treat patients for disease.

Blood type: The most important and well known blood group is ABO. Everycne's blood falls into one of 4 groups, or types: A, B, AB or O. The type depends on the presence or absence of certain substances on red blood cells. Blood types are inherited.

Components of Blood: A "part" of blood. Blood is made up of different "parts" or components: red blood cells, plasma, platelets and several types of white blood cells. Each component has its own job to do. Blood is separated into components so patients can be transfused only with what they need.

Hemophilia: A hereditary or acquired deficiency of a clotting factor(s) in blood.

Hepatitis B: Viral disease of the liver caused by the hepatitis B virus.

Hepatitis C: Viral disease of the liver caused by the hepatitis C virus.

Idiopathic Thrombocytopenic Purpura (ITP): An autoimmune disease where the body makes antibodies against its own platelets

Immunoglobulin (also called gamma globulin or immune globulin): is a substance made from human blood plasma. The plasma, processed from donated human blood, contains antibodies that protect the body against diseases.

Intravenous immunoglobulin (IVIG): is a fractionated blood product made from pooled human plasma, containing a concentrated mix of many antibodies from many hundreds of donors. It is registered for use in Canada for the treatment of a number of diseases where immunoglobulin replacement or immune modulation therapy is indicated, such as primary immunodeficiency and chronic inflammatory demyelinating polyneuropathy. IVIG is also used to treat a growing number of unregistered indications where there is some evidence for its utility. IVIG is a lifesaving therapy in appropriately selected patients and clinical circumstances.

Krever Report: Mr. Justice Horace Krever led the Commission of Inquiry on the Blood System in Canada that was established by the Government of Canada in 1993. The Inquiry investigated the blood supply

system through which infectious blood had been used in the 1980s, resulting in HIV and/or hepatitis C infection in thousands of Canadians. The Final Report of the Commission was released in 1997.

Nucleic acid amplification testing: Highly sensitive method for detecting and identifying minute amounts of genetic material.

Off-label use: Use of a therapeutic agent to treat conditions for which the relevant regulatory authority has not registered its use.

Paid: used herein to distinguish between paid/compensated/remunerated donors/donations and donations where there is no cash compensation.

Pathogen: Disease-causing agent.

Plasma: is the liquid part of blood. It is the clear, yellowish liquid portion of blood that remains after the cells and cellular components have been removed which includes the red blood cells, white blood cells and platelets. Plasma is about 90% water and it makes up 55% of blood volume. Plasma contains cells, nutrients, proteins, enzymes, hormones, salts and more. Its primary objective is to move and transport material throughout the body to areas that are in need.

Plasma-derived products (PDPs): are prepared industrially from human plasma by pharmaceutical companies and include products such as albumin, coagulation factors and immunoglobulins, which are life-saving therapeutics for several chronic and acute life-threatening diseases.

Plasma protein fractionation: Plasma proteins are separated by using the inherent differences of each protein. Fractionation involves changing the conditions of the pooled plasma (e.g., the temperature or the acidity) so that proteins that are normally dissolved in the plasma fluid become insoluble, forming large clumps, called precipitate.

Recombinant products: Products are used to manufacture a variety of proteins used in the treatment of disease. They are derived from recombinant DNA technology process of takin g a gene from one organism and inserting it into the DNA of another.

Recovered plasma: plasma which is recovered from whole blood donations.

Short, medium and long-term: 2, 5, 10+ years respectively.

Source plasma: is collected directly from the donor by the use of a plasmapheresis (apheresis) machine. Donors may be voluntary or compensated. Collecting source plasma allows up to 3 times more plasma to be collected in one sitting, and much greater frequency of donation.

Subcutaneous immunoglobulin (SCIG): infusions are given by slowly injecting purified immunoglobulin into fatty tissue just underneath the skin. SCIG can be given at home, using a mechanical infusion pump (spring loaded or battery powered) or by rapid push (a manual method that does not require a pump - infusion is pushed by hand through a syringe).

Variant CJD: A form of Creutzfeldt–Jacob disease thought to be caused by eating beef infected with BSE or mad cow disease.

Voluntary/volunteer: used herein to distinguish between unpaid/uncompensated/nonremunerated and paid/compensated/remunerated donors/donations. There is no suggestion that *any* donations are "involuntary" in the sense of being mandatory or forced.

REFERENCES

(1) Marketing Research Bureau. Clinical Uses of Plasma Products. 2018; Available at: http://marketingresearchbureau.com/plasma-industry/clinical-uses-of-plasma-products/. Accessed December, 2017.

(2) Krever H. Commission of Inquiry on the Blood System in Canada. Final Report. 1997; CP32-62/3-1997E.

(3) CADTH. CADTH Rapid Response Report: Peer Review with Critical Appraisal - Off-Label Use of Intravenous Immunoglobulin: A Review of Clinical Effectiveness. 2017.

(4) Marketing Research Bureau. The Worldwide Plasma Proteins Market 2014. February 2016.

(5) Institut national de santé publique du Québec. Utilisation des immunoglobulins non spécifiques intraveineuses et sous-cutanées au Québec 2015-2016 (Tableau 20). 2016.

(6) Marketing Research Bureau. Forecast of the Global Immunoglobulin Market 2014 – 2023. 2015.

(7) Medical Data Solutions and Services. Immunoglobulin Database Report 2015/16. 2016; Available at: http://igd.mdsas.com/wp-content/uploads/ImmunoglobulinDatabaseReport201516.pdf. Accessed November 24, 2017.

(8) National Advisory Committee on Blood and Blood Products. NAC IVIG Guidelines Hematology (2007), Neurology (2007), Solid Organ Transplantation (2010), Interdisciplinary Treatment of PID (2010). Available at: http://www.nacblood.ca/resources/guidelines/IVIG.html, 2018.

(9) Lance JR. Institut national d'excellence en santé et en services sociaux (INESSS). Utilisation des immunoglobulines intraveineuses: revue des expériences de stratégies de gestion et des données probantes disponibles. Octobre 2014. Available at: https://www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/Traitement/INESSS_Utilisation_immunoglobulines_intraveineuses.pdf.

(10) Institut national d'excellence en santé et en services sociaux (INESSS). Immunoglobulines Intraveineuses (IgIV) Usage en Neurologie. Mai 2017. Available at: http://www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/Traitement/GUO_Immunoglobulines_VF.pdf.

(11) BC Provincial Blood Coordinating Office. Intravenous Immune Globulin (IVIg) Utilization Management Program Guidelines. Available at: http://pbco.ca/images/Programs/IVIG_Provincial_Program/UM.IVIG.0007-IVIG-Utilization-Management-Program-Guidelines_V4.2.pdf. Accessed November 16, 2017.

(12) Sask Blood. Saskatchewan Immune Globulin (IVIG) Optimization Program Guidelines. September 2015; Available at: http://saskblood.ca/uploads/files/programs/sk-ivig-optimization-program/SK_IVIG_Optimization_Program_Guidelines_September2015.pdf. Accessed November 16, 2017.

(13) Best Blood Manitoba. Manitoba Intravenous Immune Globulin (IVIG) Utilization Management Program Guidelines. 2017; Available at: https://bestbloodmanitoba.ca/wp-content/uploads/2017/05/2017_Mb-IVIG_Utilization-Mgt-Prg-Guidelines-FINAL-2017.pdf. Accessed November 16, 2017.

(14) Ontario Regional Blood Coordinating Network. Intravenous Immune Globulin Toolkit for Ontario. Available at: http://www.transfusionontario.org/media/IVIG%20Toolkit_COM_2012.pdf. Accessed November 16, 2017.

(15) Nova Scotia Provincial Blood Coordinating Program. Adult IVIG Guidelines. Available at: https://novascotia.ca/dhw/nspbcp/IVIG-Docs/Adult%20IVIG%20Guidelines.pdf. Accessed November 16, 2017.

(16) Australian National Blood Authority. Immunoglobulin Governance. National Policy: Access to Government Funded Immunoglobulin Products in Australia. 2016; Available at: https://www.blood.gov.au/system/files/2016-immunoglobulin-governance-national-policy-website.pdf. Accessed November 1, 2017.

(17) UK Department of Health. Clinical guidelines for immunoglobulin use (second edition update). 2011; Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/216671/dh_131107.pdf. Accessed November 24, 2017.

(18) Kessler CM. Immune Thrombocytopenic Purpura (ITP) Treatment & Management. Medscape; 2017(November 04).

(19) American Academy of Allergy Asthma & Immunology. Eight Guiding Principles for Effective Use of IVIG for Patients with Primary Immunodeficiency. Available at: http://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20Resources/IVIG-guiding-principles.pdf. Accessed November 16, 2017.

(20) US Food and Drug Administration. Immune Globulin Intravenous (IGIV) Indications. Available at: https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm133691.htm. Accessed November 16, 2017.

(21) National Advisory Committee on Blood and Blood Products. Terms of Reference. Approved July 15, 2015. Available at: http://www.nacblood.ca/about-nac/terms-of-reference.html. Accessed 03/18.

(22) Young L. 2012 IVIG Audit. GHEST Symposium. September 28-29, 2013. Available at: http://transfusionontario.org/en/wp-content/uploads/sites/4/2013/11/IVIG_GHEST-2013.pdf.

(23) Feasby TE, Quan H, Tubman M, Pi D, Tinmouth A, So L,Ghali WA,. Appropriateness of the use of intravenous immune globulin before and after the introduction of a utilization control program. Open medicine : a peer-reviewed, independent, open-access journal 2012;6(1):28-34.

(24) Nova Scotia Health Authority. IVIG and SCIG Utilization in the Atlantic Provinces, by fiscal years (2008-2016). Available at: http://www.cdha.nshealth.ca/nova-scotia-provincial-blood-coordinating-program-4, 2018.

(25) Ontario Regional Blood Coordinating Network. Intravenous Immune Globulin (IVIG) 2012 Audit Report. Final Report. 2013-08-20. Available at:http://transfusionontario.org/en/documents/?cat=ivig.

(26) European Directorate for the Quality of Medicines & HealthCare. Optimal use of clotting factors and immunoglobulins. European Symposium Proceedings. Wilbad Kreuth, Germany; April 26-27, 2013.

(27) Charafi N., Gauthier-Darnis M., Conti C. Off-label use of intravenous immunoglobulins (IVIGs): funding mechanisms in France, Germany, Italy, Spain and the United Kingdom (EU5). ISPOR 18th Annual European Congress. November 2015.

(28) Sewell WA, Kerr J, Behr-Gross ME, Peter HH,Kreuth Ig Working Group,. European consensus proposal for immunoglobulin therapies. Eur J Immunol 2014;44(8):2207-14.

(29) Tucker Rhodes R. Immune Globulin – Controlling Supply and Demand. BioSupply Trends Quarterly Winter 2015.

(30) CADTH. CADTH Common Drug Review: Procedure for the CADTH Common Drug Review. 2014.

(31) Canadian Blood Services. Canadian Blood Services Plasma Product Selection Process. 2016;V.2016-09-14.

(32) CADTH. Hospital Formularies Decision-Making Process. 2015; Available at: https://www.cadth.ca/hospital-formularies-decision-making-process. Accessed 03/26, 2018.

(33) Canadian Blood Services. Annual Report 2016-2017: Today Changes Tomorrow. 2017.

(34) Héma-Québec. Submission to the Expert Panel on Immune Globulin Product Supply and Related Impacts in Canada. 2017.

(35) Canadian Blood Services. Submission to the Expert Panel on Immune Globulin Product Supply and Related Impacts in Canada. 2017.

(36) Bahardoust B. Open Letter to Provincial and Territorial Ministers of Health. 2016; Available at: https://giveplasma.ca/wp-content/uploads/Open-letter-to-ministers-of-health.pdf. Accessed 03/24, 2018.

(37) Prometic Life Sciences. Submission to the Expert Panel on Immune Globulin Product Supply and Related Impacts in Canada. 2016.

(38) Marketing Research Bureau. Current uses affecting the plasma industry. Available at: http://marketingresearchbureau.com/plasma-industry/current-uses-affecting-the-plasma-industry/. Accessed 03/16, 2018.

(39) European Commission, Executive Agency for Health and Consumers. An EU-wide overview of the market of blood, blood components and plasma derivatives focusing on their availability for patients. Creative Ceutical Report, revised by the Commission to include stakeholders' comments. 2015-04-08.

(40) Farrugia A. Perspectives on Self-Sufficiency of Blood-derived Therapies - Global Evolution and Realities. Third Meeting on the Italian Blood System organized by the Italian Society for Blood Transfusion and the Campus Foundation. Bologna, Italy. Oct. 18, 2014. .

(41) De Angelis V, Breda A. Plasma-derived medicinal products self-sufficiency from national plasma: to what extent? Blood Transfusion 2013 doi:10.2450/2013.019s.;(Suppl 4):11s132-s137.

(42) Australian National Blood Authority. Annual Reports, 2013-2017. Available at: https://www.blood.gov.au/pubs/1617report.v2/index.html.

(43) European Commission. Directorate-General for Health and Food Safety. Summary Minutes. Meeting between the CSL, PPTA and DG SANTE B4. 21 January 2016 . Ref. Ares(2016)6855155 - 08/12/2016.

(44) Robert P, Marketing Research Bureau. Setting the Scene for the Future of Blood and Plasma Donations. IPFA/BCA 3rd Global Symposium on the Future for Blood and Plasma Donation. 11-12 September 2017. Atlanta, GA.

(45) Sayers M. Personal Communications. 2017.

(46) Prometic Life Sciences. Prometic receives priority review status from Health Canada for Plasminogen Ryplazim. 2017; Available at: http://www.prometic.com/prometic-receives-priority-review-status-from-health-canada-for-plasminogen-ryplazim/. Accessed 03/24, 2018.

(47) Therapure Biomanufacturing. Submission to the Expert Panel on Immune Globulin Product Supply and Related Impacts in Canada. 2017.

(48) GC Biotherapeutics Inc. Plasma Derivatives. Available at: http://www.greencrossbt.com/plasma-derivatives/.

(49) Marketing Research Bureau. The Plasma Proteins Market In Canada 2015/16. 2016.

(50) Marketing Research Bureau. International Directory of Plasma Fractionators, 2015. 2017.

(51) Farrugia A, Scaramuccia D. The dynamics of contract plasma fractionation. Biologicals 2017;46(3):159-167.

(52) Ministry of Ontario. *Health Protection and Promotion Act, R.S.O. 1990, c. H.7*
R.R.O. 1990, Reg. 569: REPORTS under Health Protection and Promotion Act, R.S.O. 1990, c. H.7
Available at: https://www.ontario.ca/laws/regulation/900569. 1990 2018.

(53) Government of Canada. Notifiable diseases online. 2017-05-03; Available at: http://diseases.canada.ca/notifiable/. Accessed 03/26, 2018.

(54) Bourgeois A, Edmunds M, Awan A, Jonah LV, O., Siu W. HIV in Canada - Surveillance Report. Can Commun Dis Rep 2016;43(12):248-255.

(55) Public Health Agency of Canada. Transfusion Transmitted Injuries Surveillance System (TTISS). Available at: https://www.canada.ca/en/public-health/services/surveillance/blood-safety-contribution-program/transfusion-transmitted-injuries-surveillance-system.html. Accessed November, 2017.

(56) Canadian Blood Services. Surveillance Report 2016. Available at: https://www.blood.ca/sites/default/files/Surveillance_Report_2016_EN.pdf. Accessed December 11, 2017.

(57) Héma-Québec. Héma-Québec Annual Report 2016-2017. 2017; Available at: https://www.hema-quebec.qc.ca/userfiles/file/media/anglais/publications/AR_2016-2017_EN.pdf. Accessed Dec 14, 2017.

(58) Plasma Protein Therapeutics Association. National Donor Deferral Registry (NDDR®). Available at: https://www.pptaglobal.org/safety-quality/national-donor-deferral-registry. Accessed 03/24, 2018.

(59) European Medicines Agency. Plasma Master File (PMF) background documents. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000137.jsp&mid=WC0b01ac05800267b7#section1. Accessed 03/07, 2018.

(60) Rossi F. US and EU view on GMP Inspections - Potential Future Mutual Agreement for Inspections. IPFA/BCA 3rd Global Symposium - Future for Blood and Plasma Donation. Sept 11-12, 2017. Atlanta, GA.

(61) Hughes J, BloodSource Inc. Donor Safety, Including EU Requirements – Volumes, Frequency, Testing...IPFA/BCA 3rd Global Symposium on the Future for Blood and Plasma Donation. September 11-12, 2017. Atlanta, GA.

(62) France. Code de la santé publique - Article L5121-11. Version en vigueur au 26 février 2014. Available at https://www.legifrance.gouv.fr/affichCodeArticle.do?cidTexte=LEGITEXT000006072665&idArticle=LEGIARTI000006686077&dateTexte=&categorieLien=cid.;Article L5121-11.

(63) France. Code de la santé publique - Article L1221-3. Version en vigueur au 22 octobre 2016. Available at https://www.legifrance.gouv.fr/affichCodeArticle.do?cidTexte=LEGITEXT000006072665&idArticle=LEGIARTI000006686077&dateTexte=&categorieLien=cid. 2016;Article L1221-3.

(64) Belgium. 5 JUILLET 1994. - Loi relative au sang et aux dérivés du sang d'origine humaine. (NOTE : Consultation des versions antérieures à partir du 17-07-2002 et mise à jour au 28-08-2017) Available at: http://www.ejustice.just.fgov.be/cgi_loi/loi_a1.pl?language=fr&la=F&cn=1994070545&table_name=loi&&caller=list&F&fromtab=loi&tri=dd+AS+RANK&rech=1&numero=1&sql=(text+contains+(%27%27))#Art.4/1. 1994 18-10-1994;1994025254.

(65) Netherlands. Wet inzake bloedvoorziening (Blood Supply Law). Geldend van 01-07-2015 t/m 31-07-2016. Available at: http://wetten.overheid.nl/BWBR0009079/2015-07-01. 01-07-2015.

(66) Mahony B. The Dublin Consensus Statement 2012 on optimised supply of plasma-derived medicinal products. Blood transfusion = Trasfusione del sangue 2013;11(4):623-6.

(67) Schreiber G. Analysis of US Source Plasma Infectious Disease Residual Risk compared to Recovered Plasma Residual Risk. 2017. IPFA/BCA 3rd Global Symposium on the Future for Blood and Plasma Donation. September 11-12, 2017. Atlanta, GA.

(68) Plasma Protein Therapeutics Association. International Quality Plasma Program (IQPP). Available at: http://www.pptaglobal.org/safety-quality/standards/iqpp, 2017.

(69) Plasma Protein Therapeutics Association. Quality Standards of Excellence, Assurance and Leadership (QSEAL). Available at: https://www.pptaglobal.org/safety-quality/standards/qseal. Accessed 03/24, 2018.

(70) US Food and Drug Administration. Part 630 Requirements for Blood and Blood Components Intended for Transfusion or for Further Manufacturing Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=630&showFR=1&subpartNode=21:7.0.1.1.6.2. Code of Federal Regulations April 1, 2017;21CFR630(Title 21, Volume 7).

(71) US Food and Drug Administration. Code of Federal Regulations 21CFR610.40(a)(1). Revised as of April 1, 2017. See also WHO Guidelines Available at: http://www.who.int/bloodproducts/publications/WHO_TRS_924_A4.pdf.

(72) US Food and Drug Administration. Nucleic Acid Testing (NAT) for Human Immunodeficiency Virus Type 1 (HIV-1) and Hepatitis C Virus (HCV): Testing, Product Disposition, and Donor Deferral and Reentry Guidance for Industry (updated Dec 2017) Available at: https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/blood/ucm210270.pdf. May 2010.

(73) O'Brien SF, Yi Q, Fan W, Scalia V, Goldman M, Fearon MA. Residual risk of HIV, HCV and HBV in Canada. Transfusion and Apheresis Science 2017 June 2017;56(3):389-391.

(74) Quinti I, Visentini M, Farrugia A. Immunoglobulin Therapy in the 21st Century: The dark side of the moon. : Frontiers Media SA; 2015.

(75) World Health Organization. Annex 4 Guidelines on viral inactivation and removal procedures intended to assure the viral safety of human blood plasma products Available at: http://www.who.int/bloodproducts/publications/WHO_TRS_924_A4.pdf WHO Technical Report, Series No. 924, 2004 2004(Series No. 924).

(76) Burnouf T. Modern Plasma Fractionation. Transfus Med Rev 2007;21(2):101-117.

(77) US Food and Drug Administration. Implementation of Pathogen Reduction Technology in the Manufacture of Blood Components in Blood Establishments: Questions and Answers. Draft Guidance for Industry. 2017.

(78) Jones S. QualTex Laboratories. Infectious Disease Testing of Source Plasma Donations: Past and Future. IPFA/BCA 3rd Global Symposium on the Future for Blood and Plasma Donation. September 11-12, 2017. Atlanta, GA.

(79) O'Brien SF, Yi Q, Fan W, Scalia V, Fearon MA, Allain J. Current incidence and residual risk of HIV, HBV and HCV at Canadian Blood Services. Vox sanguinis 2012;103(1):83-86.

(80) US Food and Drug Administration. Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components. Guidance for Industry . August 2016: Available at: https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM518213.pdf.

(81) Committee for Medicinal Products for Human Use (CHMP). Reflection paper on viral safety of plasma-derived medicinal products with respect to Hepatitis E virus. European Medicines Agency June 23 2016:1-23.

(82) Young L. Hepatitis E virus infection: Epidemiology and treatment implications. PubMed Central 2015: Available at: http://pubmedcentralcanada.ca/pmcc/articles/PMC4641226/.

(83) Fearon MA, O'Brien SF, Delage G, Scalia V, Bernier B. Hepatitis E in Canadian blood donors Transfusion June 2017;57:1420–1425.

(84) Roth NJ, Schafer W, Alexander R, Elliott K, Elliott-Browne W, Knowles J, et al. Low hepatitis E virus RNA prevalence in a large-scale survey of United States source plasma donors. Transfusion 2017;57: Available at: https://onlinelibrary.wiley.com/doi/pdf/10.1111/trf.14285.

(85) Teshale E, Denniston M, Drobeniuc J, Kamili S, Teo C, Holmberg S. Decline in hepatitis E virus antibody prevalence in the United States from 1988-1994 to 2009-2010. NCBI 2015;211(3):366-373.

(86) Farcet MR, Lackner C, Antoine G, Rabel PO, Wieser A, Flicker A, et al. Hepatitis E virus and the safety of plasma products: investigations into the reduction capacity of manufacturing processes. Transfusion 2016;56(2):383-391.

(87) Yunoki M, Tanaka H, Takahashi K, Urayama T, Hattori S, Ideno S, et al. Hepatitis E virus derived from different sources exhibits different behaviour in virus inactivation and/or removal studies with plasma derivatives. NCBI 2016;44(5):403-411.

(88) US Food and Drug Administration. Revised Preventative Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Products; Guidance for Industry; Draft Guidance for Industry. 2017: Available at: https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/blood/UCM590051.pdf.

(89) Peden A, McCardle L, Head MW, Love S, Ward HJT, Cousens SN, et al. Variant CJD infection in the spleen of a neurologically asymptomatic UK adult patient with haemophilia. 2010(16):296-304.

(90) European Medicines Agency. CHMP position statement on Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products. 2010;EMA/CHMP/BWP/303353/2010: Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Position_statement/2011/06/WC500108071.pdf.

(91) World Health Organization. WHO Guidelines on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical Products. 2003: Available at: http://www.who.int/biologicals/publications/en/whotse2003.pdf.

(92) Canadian Blood Services. Travel: Does Travel Affect My Eligibility to Donate Blood? 2018: Available at: https://blood.ca/en/blood/travel.

(93) Héma-Québec. Donor Qualification: Travel; Creutzfeldt-Jakob (variant). 2018: Available at: https://www.hema-quebec.qc.ca/sang/donneur-sang/puis-je-donner/voyages/creutzfeldt-jakob.en.html.

(94) US Food and Drug Administration. Amendment to "Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Products; Guidance for Industry". U S Department of Health and Human Services 2017: Available at: https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM590051.pdf.

(95) Public Health Agency of Canada. Creutzfeldt-Jakob Disease Surveillance System. Available at: https://www.canada.ca/en/public-health/services/surveillance/blood-safety-contribution-program/creutzfeldt-jakob-disease.html. Accessed Feb 1, 2018.

(96) Héma-Québec. Submission to the Expert Panel on Immune Globulin Product Supply and Related Impacts in Canada. 2017.

(97) Flanagan P. Self-sufficiency in plasma supply – achievable and desirable? ISBT Science Series 2017;12(4):483-487.

(98) Robert P, Marketing Research Bureau. Setting the Scene for the Future of Blood and Plasma Donations. IPFA/BCA 3rd Global Symposium on the Future for Blood and Plasma Donation. 11-12 September 2017. Atlanta, GA.

(99) World Health Organization. The Melbourne Declaration on 100% Voluntary Non-remunerated Donation of Blood and Blood Components. 2009: Available at: http://www.who.int/worldblooddonorday/melbourne_declaration_VNBRD_2009.pdf?ua=1.

(100) World Health Organization. Towards 100% Voluntary Blood Donation: A Global Framework for Action. 2010: Available at: http://www.who.int/bloodsafety/publications/9789241599696_eng.pdf?ua=1.

(101) World Health Assembly (WHA). Availability, safety and quality of blood products. 2010: Available at: http://apps.who.int/gb/ebwha/pdf_files/WHA63/A63_R12-en.pdf.

(102) World Health Organization. The Rome Declaration on Achieving Self-Sufficiency in Safe Blood and Blood Products, based on Voluntary Non-Remunerated Donation. 2013.

(103) Skinner M. Blood Banks and Plasma Centers: Converging Strategies for Meeting Patient Needs. IPFA/BCA Symposium – Future for Blood and Plasma Donation. 28 September 2015. Dallas, Texas. Slides 15-22. Available at: https://ipfa.nl/UserFiles/File/WS%202015/IPFA%20BCA%20Dallas%202015/3_2_Healey_Dallas_2015.pdf.

(104) European Agency for the Evaluation of Medicinal Products. CPMP Position Statement. Non-Remunerated and Remunerated Donors: Safety and Supply of Plasma-Derived Medicinal Products. Doc. Ref: EMEA/CPMPBWP/1818/02/Final. May 30, 2002.

(105) European Commission. Commission Staff Working Document on the implementation of the principle of voluntary and unpaid donation for human blood and blood components as foreseen in Directive 2002/98/EC on setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC. SWD/2016/0130 final. April 21, 2016.

(106) European Commission Public Health. Blood, Tissues, Cells and Organs. Available at: https://ec.europa.eu/health/blood_tissues_organs/blood_en. Accessed Feb 1 2018.

(107) European Commission. Report from the Commission on the implementation of the Directives 2002/98/EC, 2004/33/EC, 2005/61/EC and 2005/62/EC setting standards of quality and safety for human blood and blood components. COM(2016) 224 final. April 21, 2016: Available at: https://ec.europa.eu/transparency/regdoc/rep/1/2016/EN/1-2016-224-EN-F1-1.PDF.

(108) Strengers PFW, Klein HG. Plasma is a strategic resource: STRATEGIC RESOURCES. Transfusion 2016;56(12):3133-3137.

(109) Mahony BO, Turner A. The Dublin Consensus Statement on vital issues relating to the collection of blood and plasma and the manufacture of plasma products. Vox Sang 2010;98(3):447-450.

(110) Mahony B, Turner A. The Dublin Consensus Statement 2011 on vital issues relating to the collection and provision of blood components and plasma-derived medicinal products. Vox Sang 2012;102(2):140-3.

(111) Chell K, Davison TE, Masser B,Jensen K,. A systematic review of incentives in blood donation. Transfusion. 2018 Jan;58(1):242-254. doi: 10.1111/trf.14387. Epub 2017 Nov 6.

(112) US Food and Drug Administration. CPG Sec. 230.150 Blood Donor Classification Statement, Paid or Volunteer Donor (Revised 2011). Available at: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-ice/documents/webcontent/ucm122798.pdf.

(113) Belgium. Agence fédérale des médicaments et des produits de santé. Arrêté royal portant exécution de l'article 20/1 de la loi du 5 juillet 1994 relative au sang et aux dérivés du sang d'origine humaine : dispositions en matière d'autosuffisance de dérivés plasmatiques. Numac : 2017020325. 2017-04-24: Available at: http://www.ejustice.just.fgov.be/cgi/article_body.pl?language=fr&caller=summary&pub_date=17-04-24&numac=2017020325.

(114) Noel S. How to reduce cost of apheresis plasma? First lessons of a benchmarking. Établissement Français du sang. 2015.

(115) Schreiber G, Kimber M. Source Plasma Donors: A Snapshot. Available at: https://www.researchgate.net/publication/321807978_Source_Plasma_Donors_A_Snapshot. Accessed March 6, 2018.

(116) Australian Red Cross Blood Service. Australian Red Cross Blood Service Business Plan 2017-2019. 2017: Available at: http://www.donateblood.com.au/sites/default/files/Business_Plan_Snapshot_Online_2017_19_5.pdf.

(117) Sanquin. Annual Report 2014: Transition - Blood and Beyond. 2014: Available at: https://www.sanquin.nl/repository/documenten/nl/over-sanquin/over-sanquin/37356/sanquin-annual-report-2014.pdf.

(118) BloodSource Inc. My BloodSource. Rewards. Health. Schedule. 2018; Available at: https://www.bloodsource.org/mybloodsource/Welcome?returnurl=%2fmybloodsource. Accessed March 6, 2018.

(119) Rossi F. International Plasma Fractionation Association. The importance of VNRBD for safe and sufficient plasma globally. 9th Seminary FIODS, 24th Sept 2016 Rome.

(120) Plasma Protein Therapeutics Association. About PPTA: Fact Sheet. October 2017; Available at: http://www.pptaglobal.org/images/Fact_Sheets/Redone/2016/Fact_Sheet_About_PPTA.pdf. Accessed January 4, 2018.

(121) Ellingson D, Sapiano MRP, Haass KA, Savinkina AA, Baker M, Chung K.W., et al. Continued decline in blood collection and transfusion in the United States - 2015. Transfusion 2017;57(2v(doi:10.1111/trf.14165)):1588-1598.

(122) Chung Koo-Whang, Basavaraju SV, Yi M, van Santen KL, Haass KA, Richard H, et al. Declining blood collection and utilization in the United States. Transfusion 2016 05/12; 2018/03;56(9):2184-2192.

(123) European Blood Alliance. Annual Report 2016. 2017: Available at: http://www.europeanbloodalliance.eu/wp-content/uploads/2017/06/EBA_AR_2016.pdf.

(124) Australian Red Cross Blood Service. Trends in red cell demand. October 19, 2016; Available at: https://transfusion.com.au/bsib_october2016_1. Accessed March 26, 2018.

(125) Canadian Blood Services. Information only: O Rh negative Red Blood Cell Utilization and Inventory Management Best Practices, Customer Letter #2014-14. 2014: Available at: https://blood.ca/sites/default/files/cl-2014-14.pdf.

(126) Sime S. LifeServe Blood Center. One Perspective on Source Plasma. IPFA/BCA 3rd Global Symposium on the Future for Blood and Plasma Donation. September 11-12, 2017. Atlanta, GA.

(127) Janssen MP, Hoeven L. R. van, Rautmann G. Trends and observations on the collection, testing and use of blood and blood components in Europe: 2001-2011. Strasbourg: European Directorate for the Quality of Medicines and HealthCare, Council of Europe 2015.

(128) Beck S. Blood Centers and Plasma Centers: Mutual Benefit. The Source Summer 2011:12-15- Available at: http://www.pptaglobal.org/images/source/The-Source_Summer-2011.pdf.

(129) Grabowski, Henry G., Manning,Richard L., An Economic Analysis of Global Policy Proposals to Prohibit Compensation of Blood Plasma Donors. International Journal of the Economics of Business 2016;23(2):149-166.

(130) European Blood Alliance. EBA Position Paper. Competition in the EU Blood Component Market. January 2009: Available at: http://www.europeanbloodalliance.eu/wp-content/uploads/2012/08/eba-position-paper-competition-in-european-blood-component-market-final.pdf.

(131) European Blood Alliance. Blood, Tissues and Cells From Human Origin. Why voluntary non remunerated blood donations are now more important than ever? p.96. ; 2013.

(132) Héma-Québec. 2016-2017 Activity Report. Direction des relations publiques 2017 Available at: https://www.hema-quebec.qc.ca/userfiles/file/media/anglais/publications/HQ%20Rapport%20d'activite%CC%81s%202016-2017-ang(1).pdf.

(133) Sher G. 2016-2017: Year in Review. CBS June 22, 2017: Available at: https://blood.ca/sites/default/files/OpenBoard_Year-End_June2017ENG.pdf slide 14.

(134) Martin A, Lavoie L, Goetghebeur M, Schellenberg R. Economic benefits of subcutaneous rapid push versus intravenous immunoglobulin infusion therapy in adult patients with primary immune deficiency. Transfus Med 2013 Feb 23;1(doi: 10.1111/j.1365-3148.2012.01201.x).

(135) Ipsos Public Affairs. Pay-For-Plasma - Canadian General Public Perspective. Final data results – weighted. Survey: June 2016.

(136) Lacetera N, Macis M. Moral and Opportunistic NIMBYism in Contested Commodities. Altruism, Community, and Markets. American Enterprise Institute.October 20, 2017.

(137) European Directorate for the Quality of Medicines & HealthCare. Blood Transfusion - Background and Mission. Available at: https://www.edqm.eu/en/blood-transfusion-mission-65.html, 2018.

(138) American Plasma Users Coalition (A-PLUS). Comments of American Plasma Users Coalition (A-PLUS) To the Food and Drug Administration December 31, 2010.

(139) Mahony B, Skinner M. Paying for Plasma: a Reality Check. For PLUS and A-PLUS. May 27, 2016. Available at: http://www.hemophilia.ca/files/Letter%20from%20PLUS%20and%20A-PLUS.pdf

(140) Mahony BO, Turner A. The Dublin Consensus Statement on vital issues relating to the collection of blood and plasma and the manufacture of plasma products. Vox Sang 2010;98(3p2):447-450.

(141) American Association of Blood Banks. About AABB. 2018; Available at: http://www.aabb.org/about/Pages/default.aspx. Accessed Feb 1 2018.

(142) European Blood Alliance. EBA fact sheet on European self-sufficiency for blood components and plasma for fractionation. Available at: http://www.europeanbloodalliance.eu/wp-content/uploads/2016/11/EBA_Pos_Paper-EU_self_sufficiency.pdf.

(143) Alliance of Blood Operators. About ABO. 2018; Available at: https://allianceofbloodoperators.org/about-abo/our-members.aspx. Accessed March 5 2018.

(144) International Federation of Red Cross and Red Crescent Societies. Position paper: Promoting safe and sustainable blood systems. 2018; Available at: http://www.ifrc.org/en/what-we-do/health/blood-services/position-paper-promoting-safe-and-sustainable-blood-systems/. Accessed March 10, 2018.

(145) Stone M, Australian National Blood Authority. Personal Communication. Feb 1, 2018.

(146) Australian National Blood Authority. IG Governance - What is BloodSTAR? Available at: https://www.blood.gov.au/system/files/What-is-bloodstar3.pdf. Accessed Jan 25, 2018.

(147) International Plasma and Fractionation Association (IPFA). IPFA: About Us. 2018; Available at: https://ipfa.nl/about-us. Accessed March 1, 2018.

(148) Strengers P. International Plasma and Fractionation Association. Goals and Value of "Strategic Independence". IPFA Asia Pacific Workshop Plasma Quality and Supply.Taipei, Taiwan. 9 March 2016.

(149) Bult JM. Plasma Protein Therapeutics Association. Strategies to encourage blood and plasma donations in Europe, PLUS meeting Dublin Jan 12, 2018. Slide 7.

APPENDIX A

TERMS OF REFERENCE

Context

Many Canadians depend on products manufactured from human plasma to treat a range of health conditions ("human plasma products"). Most of the plasma product supply used in Canada is purchased from US commercial manufacturers. In contrast, Canada's blood supply (individual blood components for transfusion in hospitals) is 100% self-sufficient through voluntary blood donation operations managed by Canadian Blood Services and Héma-Québec.

At present, there is a strong global demand for immune globulin (IG) human plasma products, which seems to be driving expansion of commercial plasma collection into new markets, including Canada. In this context, the primary CBO has raised concerns that:

- Increasingly competitive global IG market conditions may detrimentally affect the security and sustainability of the Canadian IG product supply; and
- New/expanded Canadian plasma collection operations may draw donors away from the voluntary blood donor pool to the extent that the security and sustainability of the Canadian blood supply may be detrimentally affected.

The federal government is initiating this Expert Panel on Immune Globulin Product Supply and Related Impacts in Canada ("the Panel") to provide objective expert review of the evidence related to these issues and concerns to inform future policy and practice. Its composition and mandate were developed in consultation with the PTs.

Mandate

The mandate of the Panel is to assemble, review, and assess available evidence on:

1. Supply and demand factors that may affect the security and sustainability of the IG supply for Canadians;
2. The potential impact of plasma collection activities on the security and sustainability of the Canadian blood supply, if plasma collections were to expand significantly in Canada;
3. Current and emerging international practices and lessons learned about mitigating any potential detrimental impacts on security and sustainability identified in 1 or 2 above.

In its assessments, the Panel will consider the likelihood and severity of potential impacts over short, medium, and long-term time horizons.

The Panel is not mandated to make recommendations nor to comment on current or future policy directions of governments or any other party. Decisions on policy pertaining to the blood and plasma systems in Canada remain the prerogative of governments and authorities they may designate to make or implement policy.

To guide the Panel in its assessments, Questions and Considerations have been developed (Appendix A.1). These are intended to assist, not restrict, the Panel's investigations and deliberations.

Reporting and Key Deliverables

The Panel, through its Chair, will be accountable to and report to the federal Deputy Minister of Health. Reporting will include interim updates on progress. The key deliverable will be a final report to be submitted by March 31, 2018 that includes:

- An executive summary;
- The findings, conclusions, and rationale for the conclusions of the Panel;
- An overall summary of the evidence reviewed and input received, noting any limitations about the strength of the evidence available that may have affected its findings, and how the input was viewed by the Panel.

The federal government will consult the Chair of the Panel and PTs on the disposition / release of the report, and will provide PTs with an advance embargo copy prior to any public release.

Complementary Mandates

The Provincial Territorial Blood Liaison Committee (PTBLC) provides advice and support to the Provincial and Territorial Deputy Ministers and Ministers of Health on issues affecting the blood system (excluding Québec). The Panel shall receive and consider any relevant and timely information provided by the PTBLC and/or PT officials.

External Input

To inform its deliberations, the Panel, through the Secretariat, may retain the services of independent non-government experts to provide advice or information on certain subjects within its mandate. The Panel may also, in its discretion, consult key informants, such as:

- Current Canadian operators involved in blood or plasma collection, and plasma product manufacturing;
- International experts and stakeholders;
- Representatives of Canadian patient groups dependent on human plasma products (with an emphasis on users of IG).

Composition of Panel

The Panel will consist of four members appointed by the Deputy Minister: one Chair, one Deputy Chair, and two Special Advisors who collectively possess domestic and international expertise and experience in:

- Canadian health sector context, including federal and provincial/territorial division of powers;
- International blood and plasma collection systems in public and private sector contexts;
- International supply chains, global markets, and market response mechanisms in a biological, pharmaceutical or health product context;
- Weighing diverse stakeholder interests.

Panel Responsibilities

The responsibilities of the Chair are to:

- Ensure that Panel discussions remain in line with its mandate;
- Ensure that Panel members have the opportunity to contribute;
- Collaborate with Panel members and the Secretariat;
- Provide interim updates on progress to the federal Deputy Minister of Health, as requested;
- Lead and participate in Panel meetings;
- Ensure that the report is submitted on time; and
- Submit and present the final report to the federal Deputy Minister of Health, and if requested, present at a meeting of the FPT Deputy Ministers of Health.

The responsibilities of **Panel Members** are to:

- Review relevant documents provided by or requested from the Secretariat;
- Apply their expertise and experience to provide input to the Panel's deliberations;
- Actively participate in meetings and discussions;
- Provide timely contributions to discussion and report preparation; and
- Support the chair in his/her role.

Activities expected to be part of the Panel workplan include:

- Panel meetings, including teleconference and/or face-to-face;
- Stakeholder meetings, including key informant interviews;
- Evidence-gathering, including review of documents provided by the Secretariat;

- Report-writing, including review of draft and final reports;
- Tabling of final report and presenting findings;
- Preparation for any of the above.

The Panel is encouraged to reach a consensus in its deliberations. When a consensus is not possible, the meeting record or report will reflect the diversity of opinions.

After fulfillment of its mandate, the Panel will be dissolved.

Compensation

All members are paid for their participation on the Panel. As such, these members are not eligible for indemnification. Obtaining appropriate insurance coverage under these circumstances is the responsibility of individual members if they wish to do so.

Members will be reimbursed for expenses incurred on approved travel for the Panel, such as trip costs and accommodation, in accordance with Treasury Board policy and guidelines.

Panel Secretariat

Health Canada will establish and cover the costs of a Secretariat to provide administrative and logistical support to the Panel. The Secretariat will administer Panel expenses, co-ordinate outreach activities, and expedite research, report writing and communications (including production of the final report of the Panel).

Disclosure of Interests and Affiliations

Panel members are expected to act in an unbiased, professional, respectful and fair way at all times. They may not use their position on the Panel for any private or collateral purpose. To be considered for appointment, potential Panel members are required to complete and return an *Affiliations and Interests Declaration Form,* a summary of which will be published online. In addition, Health Canada or the Chair will also ask members to make a verbal statement of their relevant affiliations and interests at the beginning of Panel meetings.

Confidentiality

To support their ability to provide well-informed advice, Panel members may receive confidential information. All panelists will therefore be required to sign a *Confidentiality Agreement* that will prohibit the disclosure of any confidential information received through participation in the Panel. The Chair will ensure that everyone participating in meetings or other communications receives clear instructions on applicable confidentiality restrictions.

The final Panel report is also considered confidential information unless or until publicly released by the federal Deputy Minister of Health. Otherwise, information gathered by the Panel may be subject to the *Access to Information Act* and the *Privacy Act*.

A member may discuss the Panel's work with the media or at conferences or other external events only with prior permission from Health Canada. All media requests related to the Panel's statements or activities will be directed to Media Relations, Health Canada, who will coordinate responses.

Security Clearance

All members are required to attain an appropriate security clearance. This may require the member to submit fingerprints to the RCMP. Health Canada provides the required forms to candidates for appointment.

Appendix A.1: QUESTIONS AND CONSIDERATIONS

The following questions and considerations are offered to guide the Panel in examining each element of its mandate.

1. **Supply and demand factors that may affect the security and sustainability of the IG supply for Canadians.**

A. Supply: There are historical examples of spikes and dips in plasma product supply/demand trends (e.g. demand for Factor VIII dropped after a non-plasma-derived replacement product was developed).
   - If the global supply market has been able to adjust to keep up with global supply/demand trends in the past, is there any reason to believe that the IG market will be unable to similarly adjust over the medium- to long-term? If so, explain what is novel about the factors driving the global long-term IG supply/demand forecast and the confidence levels in those forecasts.
   - What indicators would signal emerging issues?
   - In the event of global IG shortage, how likely is it that Canada will be unable to secure sufficient IG supply to meet Canadian demand, given current IG product supply chains?
   - Will other countries' responses to the IG market conditions (e.g. scaled-up plasma collections) improve global supply generally?

B. Demand: Canada is among the highest global users of IG product per capita.
   - To what extent do suboptimal or off-label IG usage practices materially contribute to IG demand in Canada?
   - Are there alternative technologies or treatments on the horizon for patients now using IG therapy that would materially reduce the demand for (plasma-derived) IG?

2. The potential impact of plasma collection activities on the security and sustainability of the Canadian blood supply, if plasma collections were to expand significantly in Canada.

A. Plasma collection systems co-exist with blood collection systems in a number of countries including the US, Germany, Austria, Hungary, and the Czech Republic.
   - Have plasma collection initiatives affected blood operators' ability to meet demand for fresh blood components? If so, how and to what extent?
     - What contributing factors may be relevant to the Canadian context (e.g. where blood component inventories are managed regionally/ nationally)?
   - What indicators (or levels of plasma collection activity) would signal emerging issues in the Canadian context?

3. Current and emerging international practices and lessons learned about mitigating any potential detrimental impacts on security and sustainability identified in 1 or 2 above.

The Panel could identify and highlight relevant findings related to:

A. How to optimize existing market mechanisms and infrastructure to mitigate factors that could detrimentally affect the security and sustainability of the IG product supply.
   - What actions or policy approaches have been tried elsewhere, and with what results (without/aside from changing the volume of domestic plasma collection)?

B. How to direct domestic plasma collection activities to mitigate factors that could detrimentally affect the security and sustainability of the blood donor supply.

C. Demand management mechanisms to prioritize IG access for patients for whom IG is the only or optimal therapy, in the event of a disruption in supply.

APPENDIX B

BIOGRAPHIES

Chair: Penny Ballem, MD, FRCP, FCAHS

Dr. Ballem is a haematology specialist, currently a Clinical Professor of Medicine at the University of British Columbia as well as a Professor at the Institute of Health Policy Management and Evaluation, Dalla Lana School of Public Health, University of Toronto. She obtained her MD from the University of British Columbia following an M.Sc. in Immunology from the University of Western Ontario. Dr. Ballem has held a range of senior health consulting / advisory roles for governments, chair and co-chair roles for national and international committees, and six years as Deputy Minister of Health for BC, which included being its Liaison Deputy Minister to the FPT Council of Deputy Ministers of Health regarding Canadian Blood Services. Her awards and achievements include recognition as a Fellow of the Canadian Academy of Health Sciences (CAHS) for outstanding performance in the academic health sciences in Canada.

Deputy Chair: Francine Décary, MD, PhD, MBA, IAS.A, OC, OQ

Francine Décary has a distinguished record as a haematology research scientist and blood system executive and expert. After studying medicine at l'Université de Montréal, Dr. Décary trained in blood transfusion at the New York Blood Center, and obtained a PhD in immuno-haematology from the University of Amsterdam. In 1996, she completed an Executive MBA at l'Université de Sherbrooke. By 1998, Dr. Décary was leading the Eastern Canada operations of CRC Blood Services, and subsequently founded and led Héma-Québec as Chief Executive Officer until 2011. Dr. Décary's awards for scientific and management excellence include the Prix du Québec's prix Armand-Frappier (2005), Officer of l'Ordre national du Québec (2008), and Officer of the Order of Canada (2012). Dr. Décary's Board experience includes the Canadian Society of Transfusion Medicine (chair), International Society of Blood Transfusion (chair), America's Blood Centers (Council secretary), and l'Institut national de recherche scientifique (INRS) (subcommittee chair).

Special Advisor: Merlyn Sayers, MBBCh, PhD

Dr. Sayers is President and CEO of Carter BloodCare, the community blood program in Dallas Fort Worth. He also serves on the faculty of the University of Texas Southwestern Medical Center. Dr. Sayers was previously the Medical Director at the Puget Sound Blood Center in Seattle, Washington and a faculty member at the University of Washington, Department of Hematology. Dr. Sayers' degrees were

awarded by the University of Witwatersrand, Johannesburg, South Africa. He has previously served as the Vice Chair of the Washington State Board of Health, Chairman of the FDA's Blood Safety and Availability Committee, and President of America's Blood Centers (ABC). He is extensively published on issues that include transfusion safety and donor management. He is the most recent recipient of ABC's Lifetime Achievement Award.

Special Advisor: Patrick Robert, Ph.D.

Patrick Robert, Ph.D. is the president of the Marketing Research Bureau, Inc. since 1995, a market research firm specializing in collecting and analyzing data on blood and plasma products markets worldwide. Dr. Robert has thirty years of experience in the non-profit and commercial blood and plasma sectors (including: WHO (1972), the French Social Studies Corporation (SEDES) (1975), and the OECD (1976)). In 1977 he became the Administrator of the Blood Transfusion Department of the International Federation of Red Cross and Red Crescent Societies in Geneva, Switzerland. In 1987, he joined Bayer Corporation as Marketing Research Manager of Plasma Products Division (now Grifols). Dr. Robert holds a doctorate in Health Economics from University of Aix en Provence, France, and a Master of Public Administration from Cornell University, USA. He also studied in Tübingen, Germany for two years. He has published several articles on health care organization, and numerous market studies in the area of blood and plasma.

From Left to Right: Patrick Robert, Francine Décary, Penny Ballem and Merlyn Sayers

APPENDIX C

GROUPS OR INDIVIDUALS ENGAGED BY PANEL OR CHAIR

This appendix includes the names of organizations and/or individuals who met with the Panel and/or Chair during the course of the Panel's work. Categories included in this appendix are:

- Groups that presented to the Panel;
- Organizations that submitted statements to the Panel and/or participated in roundtable discussions;
- Provincial and Territorial Blood Liaison Committee (as of February 2018);
- Key Informants;
- National Advisory Committee (as of February 2018).

Groups that presented to the Panel

Company	Title	Name
Canadian Blood Services	CEO	Dr. Graham Sher
	Vice President, Public Affairs	Jean-Paul Bédard
	Director, Strategy Planning and Portfolio Management	Mathias Haun
Canadian Plasma Resources	CEO	Dr. Barzin Bahardoust
	Consultant	Jim Pimblett
CSL Behring	Senior Medical Director	Toby L. Simon
	Director Senior Business Services	David Confessore
Grifols Canada Ltd.	General Manager	Mary Hughes
Héma-Québec	Vice President, Medical Affairs and Innovation	Dr. Marc Germain
Prometic	Vice-President Plasma Technologies	Bill Bees
Therapure Biopharma Inc	President, ProductsCo Biologics (now Evolve Biologics)	Blaine Forshage
	Head of Plasma Operations	Mark Krause

Organizations that submitted to the Panel and/or participated in roundtable discussions

- Alpha-1 Canada
- Blood Watch
- Canadian Federation of Nurses Unions
- Canadian Health Coalition
- Canadian Hemophilia Society
- Canadian Immunodeficiencies Patient Organization
- Canadian Labour Congress
- Canadian Rheumatology Association (CRA)
- Canadian Society of Allergy and Clinical Immunology (CSACI)
- Canadian Union of Public Employees (CUPE)
- Council of Canadians
- Hereditary Angioedema Canada
- Immunodeficiency Canada
- Network of Rare Blood Disorder Organizations
- New Brunswick Health Coalition
- Ontario Regional Blood Coordinating Network (ORBCoN)

Provincial and Territorial Blood Liaison Committee (as of February 2018)

Name	Title	Division	Department
Carol Amirault	Director	Territorial Health Services	Department of Health and Social Services
Brian Bertelsen	Policy Analyst	Health Policy and Programs	Department of Health and Wellness
Marina Hamilton	Program Manager, PT	Provincial Blood Coordinating Program	NSHA
Judy Hoff	Director	Transfusion Medicine	Saskatchewan Health
Dai Kim	Manager	Provincial Agencies Trillium Gift Of Life Network / Blood & Specialized Programs (PATBS)	Ministry of Health and Long-Term Care
Glenna Laing	Director, Provincial Services Unit	Pharmaceutical and Supplementary Benefits	Alberta Health
Sonia Marchand	A/Manager, Laboratory Services		Government of Nunavut
Daphne Osborne	Program Manager	Provincial Blood Coordinating Program	Department of Health and Community Services
Emily Scrivens	Policy Analyst	Department of Health and Social Services	Government of Yukon H1
Robert Shaffer	Executive Director, Cancer & Diagnostic Services (CDS)	Regional Policy and Programs	Manitoba Health, Healthy Living and Seniors
Jane Stafford	Healthcare Consultant	Health Services Division	Health
Wendy Vowles	Director, Blood Services	Laboratory, Diagnostic & Blood Services Branch	Hospital, Diagnostic and Clinical Services Division

Key Informants		
Name	**Position**	**Organization**
Bult, Jan	President and CEO	Plasma Protein Therapeutics Association (PPTA)
Barotine-Toth, Dr. Klara	Director of QA-QC	Hungarian Blood Transfusion Service (HNBTS (OVSZ))
Brill-Edwards, Dr. Michele	Independent Hospital & Health Care Professional	University of Toronto, Faculty of Medicine
Cervenakova, Larisa	Medical Director	Plasma Protein Therapeutics Association
Doucette, Dr. Doug	CSHP President Elect and External Liaison and Regional Pharmacy Clinical Manager	CSHP and Horizon Health Network
Hall, Frances	Director, Office of Pharmaceuticals Management Strategy	Strategic Policy Branch, Health Canada
O'Byrne, Patrick	Executive Director	Saskatchewan Disease Control Laboratory, Ministry of Health
Reynolds, Karen	Executive Director, Office of Pharmaceuticals Management Strategy	Strategic Policy Branch, Health Canada
Rongve, Dr. Ian	Assistant Deputy Minister Hospital, Diagnostic and Clinical Services Division	Ministry of Health, British Columbia
Roy, Myrella	Executive Director	Canadian Society of Hospital Pharmacists
Sabourin, Pierre	Assistant Deputy Minister	Health Products and Food Branch, Health Canada
Schreiber, George	Director Epidemiology Source & International Affairs	Plasma Protein Therapeutics Association
Sher, Dr. Graham	CEO	Canadian Blood Services
Stone, Michael	Deputy General Manager and General Counsel	National Blood Authority in Australia
Strengers, Paul	Executive Director	International Plasma Fractionation Association (IPFA)

National Advisory Committee Members (As of February 2018)

British Columbia

Dr. Robert Coupland
Kelowna General Hospital
Kelowna, BC

Dr. Dana Devine
Canadian Blood Services
Vancouver, British Columbia

Dr. Doug Morrison
Fraser Health Transfusion Medicine
New Westminster, British Columbia

Alberta

Dr. Meer-Taher Shabani-Rad
Calgary Laboratory Services
Foothills Medical Centre
Calgary, Alberta

Dr. Susan Nahirniak
University of Alberta Hospital
Edmonton, Alberta

Saskatchewan

Judy Hoff [Co-Chair]
Saskatchewan

Dr. Donna Ledingham
Regina Qu'Appelle Health Region
Regina, Saskatchewan

Ms. Shelley Stopera
NAC Coordinator / Program Consultant

Dr. Oksana Prokopchuk-Gauk
Saskatoon Health Region
Saskatoon, Saskatchewan

Manitoba

Dr. Debra Lane
Canadian Blood Services
Winnipeg, MB

Dr. Brian Muirhead
Health Sciences Centre
Winnipeg, Manitoba

Wendy Peppel
Manitoba Health
Winnipeg, Manitoba

Ontario

Lindy McIntyre
Canadian Blood Services
Ottawa, Ontario

Dr. Chantal Pambrun
Canadian Blood Services
Ottawa, Ontario

Dr. Katerina Pavenski
St. Michael's Hospital
Toronto, Ontario

Dr. Alan Tinmouth
Ottawa Hospital
Ottawa, Ontario

Rick Trifunov
Canadian Blood Services
Ottawa, Ontario

Dr. Kathryn Webert
Canadian Blood Services
Ancaster, Ontario

Lindy McIntyre
Canadian Blood Services
Ottawa, Ontario

Québec

Dr. Vincent Laroche
Centre hospitalier affilié universitaire de Québec
Québec City, Québec

Atlantic provinces

Dr. Jennifer Fesser [Co-Chair]
Queen Elizabeth Hospital
Charlottetown, Prince Edward Island

Dr. Lakshmi Rajappannair
Horizon Health Network
Saint John, New Brunswick

Dr. Irene Sadek
Capital District Health Authority
Halifax, Nova Scotia

Dr. Sudeep Shivakumar
Capital District Health Authority
Halifax, Nova Scotia

Dr. Lucinda Whitman
Eastern Health
St. John's, Newfoundland

APPENDIX D

PATIENT GROUPS

METHODOLOGY

- Eleven patient organizations were invited to submit written input on issues relevant to the Expert Panel on Immune Globulin Product Supply and Related Impacts in Canada (see List 1). Six organizations responded in October 2017: Alpha-1 Canada; Canadian Hemophilia Society; Canadian Immunodeficiencies Patient Organization (CIPO); Hereditary Angioedema Canada (HAE); Immunodeficiency Canada; and Network of Rare Blood Disorder Organizations (NRBDO).
- Invitations were sent September 27, 2017 to selected Patient Groups to inform them of the work of the Expert Panel on Immune Globulin Product Supply and Related Impacts in Canada (the Panel), to request their input on the issue, and to invite them to participate in a teleconference hosted by the Panel's Chair and Deputy Chair.
- Invitations were sent to organizations representing users of immune globulins and other plasma products, including those dependent on rare/orphan plasma products.
- To help focus their answers on issues of most interest to the Panel, and to facilitate our review of their submissions, groups were asked to respond to questions in their submission (see List 2).
- Submissions were not to exceed three pages in length, and were to be sent electronically by October 6, 2017. Staff followed up the first week of October to confirm that organizations had received the invitation and again the week of October 10, 2017 with organizations that had yet to respond.

List 1: Identified patient groups and received submissions

Alpha-1 Canada*
Alzheimer Society of Canada
BC Hemophilia Society
Canadian Hemophilia Society*
Canadian Immunodeficiencies Patient Organization*
Canadian Liver Foundation
Canadian Organization of Rare Disorders
Guillain-Barre Syndrome Foundation of Canada
Hereditary Angioedema Canada (HAE)*
Immunodeficiency Canada*
Network of Rare Blood Disorder Organizations*

*Groups that responded

List 2: Questions

1. Please identify the name of your organization and provide the name/email of the contact person for the submission.

2. Please briefly describe the disorder/disease(s) you represent that are treated by plasma-derived products and the interest of your organization as it relates to the plasma product supply.

3. Patient demographics (if available). Please specify your source(s) of data, e.g. patient registries. Data of interest includes:

   + Number of patients in Canada

   + Extent of use of immune globulin product(s) (i.e. % of patients dependent on immune globulins, if known)

   + Extent of use of other plasma-derived products (please specify product(s) and % of patients dependent on plasma products, alone or in combination with immune globulin).

   + Summary of any patient-cost issues related to key plasma-derived products above (i.e. whether covered by drug plans)

   + Do you track experimental clinical trials that could affect the use of plasma-derived products for your members' conditions (i.e. that could replace use of immune globulins, or that are new indications for plasma products)? If so, please provide details of trials, products tested, and any results available.

4. Please provide any formal position or policy statement that has been developed by your organization related to the mandate of the Panel (this may include published editorial or opinion pieces). If such documents exist, please attach or paste below, specifying the source and date.

   + If not stated explicitly in the statement, please explain the rationale and evidence on which it was based. This might include input from membership of your organization, the public, scientific evidence or public policy documentation behind your position, if available.

5. Do you have any evidence of factors considered by patients or clinicians when making treatment/prescription decisions (e.g. results of member or stakeholder surveys)?

6. Please provide succinctly additional information or evidence related to the mandate of the Panel that you wish to share with the members of the Panel.

Alpha-1 Antitrypsin Deficiency Canada Inc. (Alpha-1 Canada)

Providing information and support for Alpha-1 Antitrypsin Deficiency
Soutenir, informer et éduquer les personnes atteintes d'un défi cit en alpha-1-antitrypsine

October 6, 2017

Attn: Expert Panel on Immune Globulin Product Supply and Related Impacts in Canada

Thank you for the opportunity to contribute to the Expert Panel's review of plasma in Canada. The following submission includes information requested by the panel and our organization looks forward to participating in further consultations throughout the expert panels mandate.

Organizational Profile

Angela Diano, Executive Director
Executive Director, Alpha-1 Antitrypsin Deficiency Canada Inc.
Tel/Tel: 519.566.5839
www.alpha1canada.ca

Alpha-1 Antitrypsin Deficiency Canada Inc. (Alpha-1 Canada) is a national not-for-profit organization committed to providing information and support to people affected by Alpha-1 Antitrypsin Deficiency; informing the medical community about Alpha-1 Antitrypsin Deficiency; and to generate broad awareness about this genetic liver, lung and skin disease.

Alpha-1 Canada is a registered non-for-profit charitable organization governed by a volunteer board of directors and assisted by a medical advisory committee consisting of Canada's top researchers and clinicians in the field of Alpha-1.

Patient Overview and Treatment Factors

Alpha-1 Antitrypsin (A1AT) Deficiency is a genetic condition passed from parents to their children through their genes. Because Alpha-1 is genetic, Alpha-1 lung disease is commonly called "genetic COPD." According to Canadian Thoracic Society[1] (CTS), there are approximately 5000 individuals in Canada are affected by severe A1AT deficiency, however, the disease has only been diagnosed in less than 1000 Canadians. The most frequent cause of death in non-smoking individuals with severe A1AT deficiency is liver disease and the development of cirrhosis. For those with lung disease, it is most severe in individuals who smoke or have had a history of smoking, however, as this is a genetic disease these are factors (i.e., smoking) exacerbate the progress of the disease.

While there is no cure for this rare genetic disease, treatments are available to improve a patient's quality of life and length of life in specific medical circumstances. Augmentation therapy is currently commercially available with an intravenous protease inhibitor derived from human plasma. The drug, Prolastin-C, is approved by Health Canada for treatment of patients who clinically demonstrate panlobular emphysema and have congenital deficiency of Alpha-1 antiprotease.

[1] The Canadian Thoracic Society (CTS) is Canada's national specialty society for respirology bringing together over 1,000 members representing specialists, physicians and researchers as well as healthcare professionals from a variety of disciplines working in respiratory health.

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Currently, the only accessible therapy through provincial insurance plans in Canada for Alpha-1 Antitrypsin Deficiency is Prolastin-C, produced by Grifols. It is available on the public insurance plans of four provinces (British Columbia, Alberta, Manitoba and Quebec) and costs approximately $90,000 per patient, per year.

There continue to be clinical studies on the effectiveness of Prolastin-C. This includes a clinical study conducted between 2006-2012 that involved 180 patients from 13 countries. It was a randomised, double-blind, placebo-controlled trial that provided additional evidence to support the medical benefit to patients diagnosed with Alpha-1 and receiving Prolastin-C[2]. Additionally, the Alpha-1 Canadian Registry tracks and promotes current clinical trials, which can be found here.

In addition to Prolastin-C, Zemaria (produced by CSL Behring) and Glassia (produced by Shire) are therapies currently marketed in other countries. Zemaira has recently received Health Canada approval, however, it currently not marketed in Canada. There are also ongoing Canadian based clinical trials involving Glassia.

For testing and treatment of Alpha-1, Health Professionals in Canada rely on advice developed by the Canadian Thoracic Society, produced under the auspices of the CTS Canadian Respiratory Guidelines Committee.

Additional Information

The challenge that Alpha-1 Canada and its patients face is limited data due to inconsonant and limited testing in provinces (i.e., reimbursement for lab costs) and availability of treatment options. As referred to as part of the submission, the only Canadian sources for information is the CTS Guidelines or the Alpha-1 Canadian Registry, who have a limited patient base to collect data from.[3] As a rare disease, patients suffering from Alpha-1 Antitrypsin Deficiency have few options for treatment outside of the four provinces where Prolastin-C is covered. For instance, in Ontario, there are approximately 90 patients with prescriptions for Prolastin-C but only 40 of them having filled the prescription. Without public coverage for their treatment, those 40 individuals are participating in clinical studies, have private insurance or are paying out of pocket. In some cases, individuals prescribed a therapy in a province without coverage will even relocate to jurisdictions where there Prolastin-C is listed on the public formulary, but will have to start their health care journey anew in that province without any guarantee that they will receive the therapy.

[2] Eur Respir J 2009; 33: 1345–1353

[3] The Alpha-1 Canadian Registry is a confidential database where Canadian researchers store information shared with them by patients with alpha-1 antitrypsin deficiency. Gathering this information in one place allows researchers to learn more about the disease and how it affects patients. The Canadian Registry was established by Dr. Ken Chapman in 1999 to facilitate research initiatives and promote the development of treatment for alpha-1. Physicians use the registry to track patient progress, which is important for improving the quality of life for those living with this condition. The registry also keeps patients up to date on research advances, treatment options, events, and opportunities to participate in clinical trials.

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What we do know is that any therapy brought to market is plasma based and will continue to rely on plasma collected from donors outside of Canada. The therapies marketed in Canada and internationally are all plasma derived products, and it is anticipated that any future products brought forward to Canada would be the same. However, it should be noted that the only therapy marketed in Canada is not derived from plasma donated by Canadian sources. Furthermore, according to a position statement by CTS, "although the Canadian plasma that remains after various plasma proteins have been extracted for therapeutic use is potentially available as a raw material for the production of Prolastin, it is not being used to relieve the worldwide shortage or to make more of the product available for clinical trials."[4] As such, it is unclear how and why there is unique treatment of this particular plasma therapy compared to others, such as hemophilia.

Furthermore, of particular challenge is that there is inconsistent treatment of rare, orphan drugs, across Canada in terms of the approval processes as well as coverage options. And, without the benefit of increased coverage for therapies (old or new) that have a medical benefit to Alpha-1 Patients, there will be a challenge in collecting more, relevant data.

As such, Alpha-1 Canada would make the following recommendations for the Expert Panel to consider:

- Given that Canadian Blood Services is the steward of fractionated blood products in Canada, it would be helpful to review how CBS manages fractionated blood products to better understand how both CBS and Health Canada can support therapies for rare diseases, even when those therapies are developed with plasma not derived Canadian donors.
- Before any substantive changes to the plasma collection system in Canada is made, the federal government should complete the required processes to enact regulations to bring into force the National Orphan Drug Framework. Until this is done, it will be difficult to understand the need and impacts to Canadian plasma collection and regulatory system with more accessible drugs for rare disorders in Canada.

Lastly, Alpha-1 Canada would benefit from a better sense of the mandate of the Expert Panel and the specific drivers for review of the plasma system, under the direction from Health Canada. While our organization is grateful for the opportunity to participate, having a clear sense of the purpose and scope of the expert panels review would allow Alpha-1 to provide as much relevant information as possible. At its core, our organization believes that any review should focus on patient need and how the system is performing for patients first and foremost.

Thank you again for the opportunity to provide information to the panel, and we look forward to further discussions on October 27th, 2017.

[4] A position statement of the Canadian Thoracic Society. Can Respir J 2001; 8(2): 81-88

ALPHA-1 CANADA

Alpha-1 Antitrypsin Deficiency Canada Inc. (Alpha-1 Canada)

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Soutenir, informer et éduquer les personnes atteintes d'un déficit en alpha-1-antitrypsine

Appendix 1

Alpha-1 Canada Official Statement Regarding Paid Plasma Donation in Canada

Alpha-1 Canada supports the continuation of paid plasma donation (PPD) in Canada and encourages all governmental bodies to provide ongoing support for the maintenance of such practices. Plasma collection is essential for the production of many life-saving medical therapies including alpha1-proteinase inhibitor, which is a valuable treatment option for Canadians diagnosed with Alpha-1 Antitrypsin Deficiency.

Paid Plasma Donation in Canada is regulated by Health Canada and the US FDA and poses no increased risk to Canadians. Over the last 25 years, no infectious disease transmission has been related to this process. If PPD is banned in Canadian provinces, then Canada will be dependent on importing an increased amount of plasma and plasma-derived products from other countries, many of which obtain their plasma from PDD.

Alpha-1 Canada recognizes and commends Canadian Blood Services on their efforts to develop a plasma plan in 2017 to significantly increase the amount of plasma Canadian Blood Services collects from voluntary, non-remunerated Canadian donors.

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Canadian Hemophilia Society
Help Stop the Bleeding
Société canadienne de l'hémophilie
Arrêtons l'hémorragie

Submission to the Expert Panel on Immune Globulin Product Supply and Related Impacts in Canada

Submission of the Canadian Hemophilia Society, 301--666 Sherbrooke St. West, Montreal, Quebec, H3A 1E7. Contact person: David Page, National Executive Director, Canadian Hemophilia Society, dpage@hemophilia.ca, 1--418--884--2792

The Canadian Hemophilia Society (CHS) is a patient organization representing people with inherited bleeding disorders, namely: hemophilia A and B, von Willebrand disease (VWD), rare factor deficiencies and inherited platelet disorders. While most patients with hemophilia A and B are now treated with recombinant clotting factors, many with other bleeding disorders continue to be treated with plasma--derived medicinal products.

The number of patients with inherited bleeding disorders are[1]: hemophilia A and B: 3822;; von Willebrand disease: 4180;; rare factor deficiencies (I, II, V, V&VIII, VII, X, XI, XIII);; and other hereditary bleeding disorders including platelet disorders: 1899.

Immune globulin products are not used to treat inherited bleeding disorders. Recombinant therapies are available for hemophilia A and B, and factor XIII deficiency, but are not available for VWD, most rare factor deficiencies or platelet disorders. Recombinant factor VIII is the standard treatment for hemophilia A and represents more than 90% of the products infused. Plasma--derived factor VIII containing von Willebrand factor is, however, used for specific indications, notably immune tolerance induction to treat inhibitors to factor VIII, a serious treatment complication. In hemophilia B, recombinant factor IX is used in 90% of cases.; plasma--derived factor IX in the balance. Serious bleeding in VWD is treated with plasma--derived von Willebrand factor; less serious bleeding with desmopressin. Rare factor deficiencies are treated with plasma--derived factor concentrates and/or fresh frozen plasma. Platelet function disorders are treated with a number of therapies including platelets.

The key factors in clinician/patient choice in clotting factor concentrates are efficacy and the risk of developing an inhibitor (neutralizing antibody) to the infused treatment, not the origin of the plasma used in manufacturing.

Of the 11 plasma--derived clotting factor concentrates used in Canada, only two (Humate P® for VWD and Riastap® for fibrinogen deficiency) are manufactured from plasma from unpaid donors collected by Canadian Blood Services and Héma--Québec. The remaining nine clotting factors are made by a number of multi--national pharmaceutical companies using plasma from paid U.S. donors.[2] Because many of these companies are unlikely to have fractionation contracts with CBS and Héma--Québec, collecting more plasma from Canadian donors is unlikely to change this situation significantly.

The cost of the products described above, whether recombinant or plasma-derived, is reimbursed through the plasma protein budgets managed by Canadian Blood Services and Héma-Québec and made available to patients at no direct cost.

The CHS closely follows clinical trials of innovative therapies for inherited bleeding disorders and regularly updates this information in a section of its website called *Products in the Pipeline*.[8]

The CHS Policy on Paid Plasma Donations was approved by the CHS Blood Safety and Supply Committee on March 11, 2013, and adopted by the CHS Board of Directors on May 26, 2013. It is an addition to the complete CHS Policy on Blood, Blood Products and their Alternatives, adopted in 2003 and reviewed annually.[9] The Policy on Paid Plasma Donations states:

- Given that 80% of the Canadian and world supplies of plasma-derived products are manufactured from the plasma of paid donors, mainly from the U.S.;
- Given that Canadian Blood Services and Héma-Québec are increasingly dependent on U.S. source plasma from paid donors for the supply of plasma-derived products and that they have no plans to become, at best, more than 30% sufficient in plasma for immunoglobulin (Ig) supply from Canadian non-paid donors;
- Given the worldwide shortage of plasma-derived products;
- Given that many plasma-derived products used in the treatment of bleeding disorders (von Willebrand disease, rare clotting factors, inhibitors) are already manufactured from U.S. source plasma from paid donors;
- Given that plasma-derived products are life-saving therapies for a number of other rare blood diseases that affect thousands of Canadians;
- Given that, with the exception of factors VIII, IX and XIII, there are no recombinant alternatives for these products;
- Given that effective donor selection and testing technologies are applied to both paid and non-paid donations;
- Given that, in addition, highly effective viral elimination/reduction steps are applied to plasma-derived products;
- Given that plasma-derived products from paid donors have not been shown to transmit HIV, HBV or HCV in more than 20 years;
- Given that plasma collection sites in Canada where donors are paid have operated under Health Canada and U.S. FDA regulation and oversight for many years;

The Canadian Hemophilia Society takes the position that:

1. Plasma-derived products in adequate supply from both paid and non-paid sources are essential to the health of thousands of Canadians and, indeed, hundreds of thousands of people around the world;
2. Plasma-derived products manufactured following Standard Operating Procedures and Good Manufacturing Practices are of equally high quality from both paid and non-paid donors;
3. The collection of source plasma from paid donors in a properly regulated environment is not a patient safety issue;
4. CBS and Héma-Québec should make all reasonable efforts to increase the quantity of Canadian plasma for fractionation from non-paid donors and the number and quantity of plasma-derived products made from this plasma;
5. In the absence of any realistic strategy to significantly increase the Canadian contribution to the world supply from non-paid donations, and when Canada relies

almost entirely on paid donors from the U.S. for life--saving plasma--derived products, it is not defensible to reject paid donor practices on ethical grounds;.

6. Any endeavour to collect plasma for plasma--derived products from paid donors in Canada must respect the highest regulatory standards. Health Canada should make these standards known to Canadians and report to Canadians on a regular basis the results of their collection site inspections, including transfusion--transmissible infection rates among donors. CHS will monitor these reports and endeavour to hold the regulator to account.
7. Any endeavour to collect plasma for plasma--derived products from paid donors must not affect the ability of Canadian Blood Services or Héma--Québec to collect whole blood, platelets and plasma from non--paid donors to meet the needs for fresh blood components. Canadian Blood Services and Héma--Québec should report to Canadians on a regular basis the impact of paid plasma collections on their ability to meet the needs of Canadian patients.
8. The health of donors should not be compromised by their donations, paid or non--paid. Donors should not be exploited by any individual or organization. Measures and initiatives taken to encourage blood and plasma donations should not overwhelm the capacity of the donor to make an informed decision about whether to donate.
9. Patients whose continued health is dependent on the use of blood components or plasma--derived products have a right, through their representative organizations, to be consulted on any issue which may have an impact on the safety, efficacy or supply of the treatment they receive. Health authorities should ensure that robust mechanisms are in place to ensure that this happens.

More information is available from the "CHS Policy on Paid Plasma Donations, Background Document." The Canadian Hemophilia Society is a signatory to *The Dublin Consensus Statements* of 2011 and 2012.[iv] [v]

Conclusion

The CHS recognizes that the pain and suffering caused by the tainted blood tragedy of the 1970s and 1980s are not forgotten. The issue of payment for plasma donation remains a controversial and emotional one;; however, the CHS stands by its evidence--based positions. Plasma--derived medicinal products (PDMPs) are of equivalent safety, whether manufactured from paid or unpaid donations. In a perfect world, all donations of plasma would be unpaid;; realistically, however, payment for plasma donation is essential to the Canadian and world supply of these medicines. It is no more or less ethical to pay Canadian donors than it is to pay American donors. Indeed, what would be unethical is any action that would deny an adequate supply of essential medicines to patients. Evidence from the United States has shown that two systems—one to collect fresh blood components from unpaid donors and a second to collect source plasma for subsequent manufacturing into PDMPs—can co--exist. They should work cooperatively. Public--private collaboration between reputable companies in the plasma collection/fractionation field and the two Canadian Blood Establishments, CBS and Héma--Québec, should be explored and expanded.

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[i] World Federation of Hemophilia Global Survey 2015. http://www1.wfh.org/publications/files/pdf--1669.pdf
[ii] Clotting Factor Concentrates. Website of the Canadian Hemophilia Society. http://www.hemophilia.ca/en/bleeding--disorders/clotting--factor--concentrates/
[iii] Products in the Pipeline. Website of the Canadian Hemophilia Society. http://www.hemophilia.ca/en/safe----secure--blood--supply/products--in--the--pipeline/

[v] CHS Policy on Blood, Blood Products and their Alternatives. http://www.hemophilia.ca/en/about--the--chs/public--affairs/chs--policy--on--blood----blood--products--and--their--alternatives/
[vi] CHS Policy on paid plasma Donations. Background document. http://www.hemophilia.ca/files/Background%20document%20for%20policy%20on%20paid%20plasma%20donations%2029--05--2013.pdf
[vii] The Dublin Consensus Statement 2011. Vox Sang. 2012 Feb; 102(2):140--3. doi: 10.1111/j.1423--0410.2011.01528.x. Epub 2011 Aug 1.
[viii] The Dublin Consensus Statement 2012. Blood Transfus. 2013 Oct; 11(4): 623--626. doi: 10.2450/2013.0044--13

Expert Panel on Immune Globulin Product Supply and Related Impacts in Canada
REQUEST FOR INPUT: PATIENT / PRODUCT USER GROUPS SUBMISSION

The Canadian Immunodeficiencies Patient Organization (CIPO)

1. Contact for submission: Whitney Goulstone, Executive Director whitney.goulstone@cipo.ca

2. Our organization represents patients living with primary immunodeficiencies diseases (PI). CIPO's membership is over 1600 patients, care givers and healthcare professionals across Canada. PI consists of over 340 different genetic disorders is categorized by specific abnormalities or defects of the immune system. PI patients are born with part of their immune either broken or not working properly. For the majority of these patients, Immune Globulin replacement (IG) therapy remains the only option. Ig therapy given intravenously (IVIG) or subcutaneously (SCIG) is required in patients with certain PI diseases "characterized by absent or deficient antibody production and, in most cases, recurrent or unusually severe infection .... Replacement therapy for agammaglobulinemia and hypogammaglobulinemia in well-described immunodeficiencies such as Xlinked agammaglobulinemia (XLA) or common variable immunodeficiency (CVID) is necessary and life-saving" (Elena E. Perez, 2017).

   Due to the continual life-long use of IG for PI patients, and the growing PI population (see point 3), CIPO advocates strongly for a diverse and sustainable supply of plasma and products in Canada.

3. Canada unfortunately does not have a patient registry for Primary Immunodeficiency (PI) despite efforts made by Dr. Christine McCusker at McGill University.
   - The most recent data from the Immune Deficiency Foundation in the United States, states that the relevance of PI is far more than estimated at 1 in 12,000 (IDF, 2017). A new study done at McMaster University concludes that there are 5,354 new PI cases annually in Canada (Robert B. Hopkins, 2017). Primary immunodeficiency affects roughly 50,000 Canadians, although %70 remain underdiagnosed (IPOPI, 2016).
   - 93% of diagnosed immunodeficiency patients in Canada are currently accessing this life-saving treatment (Tough, 2017)
   - IVIG and SCIG products are currently purchased by CBS and covered by the provinces. The current cost to patients is the ancillary supplies in home therapy.

- CIPO does track clinical trials relating to PI. Current and recent Health Canada trials have primarily been in SCIG domain. There have been a few in the rarer conditions.

4. CIPO does have a formal policy statement on compensated plasma. We have attached it to this submission. This statement reflects our advocacy efforts for sustainability and diversity of products and supply in Canada.

5. The results of the CIPO membership survey of 2016 show that patients do not choose their method of treatment. Currently, among PI patients %51 are using SCIG and %42 IVIG (Tough, 2017).
    - This number is increasing each year in conjunction with the 5,354 newly diagnosed cases annually.

6. Canadian Blood Services currently only supplies %17 of Canadian plasma needs and that number is expected to drop to %9 by 2021 if the collection does not increase dramatically. We support CBS' current proposal to increase plasma production in Canada to %50 sustainability within 5 years. We believe however, that it is an ambitious goal, and even unsustainable unless a compensation model is used in conjunction with the current volunteer donor model.
    - There has been a compensation model co-existing with the volunteer donation model in Manitoba for the past two decades, without any direct negative impact to the voluntary donor pool. They have shown to pull from two very different donor bases, those wishing for compensation and those wishing to "do good".
    - Since the safety of the industry and the end-products are no longer an issue, is the issue of compensation an ethical issue in Canada? Patients are already receiving product that is made from plasma from compensated US donors. It is CIPO's position that Canadian patients would rather receive Canadian plasma from compensated Canadian donors than US plasma from compensated US donors.
    - CIPO, and our international associations, are aware and concerned about the potential usage in China and Indian and growing awareness and diagnosis emerges. The US currently produces %80 of the world's plasma supply.

CIPO's position is fully in the best interest of PI patients in Canada for a sustainable and diverse supply of IG therapy and products.

STATEMENT ON PAID PLASMA PRODUCTS

The Canadian Immunodeficiencies Patient Organization, CIPO, is a registered charity representing patients with Primary Immune Disorders (PI) across Canada.

There are currently and estimated 50,000 people living with PI in Canada. Plasma-derived therapy is the only treatment option currently available, along with antibiotics, to PI patients. Canada is the largest user of IVIg (intravenous plasma treatment) per capita.

As end users of plasma-derived products, key concerns remain the same. These are:

1. The vast majority of PID patients in Canada, are already using plasma-derived product from U.S. paid donors. There has been no problems or issues with these products and the safety regulations in place are considered safe by blood system regulators around the world. Currently, our patients feel safe with their product. We want them to continue in this regard.
2. Not allowing paid plasma donations in Canada will encourage Canada's over-reliance on the U.S for plasma. We are concerned that only 3 of some 30 plasma-derived products used by Canadians are manufactured in whole or in part by plasma collected from unpaid donors by CBS and Héma-Quebec.
3. CIPO understands the fear of the past, but over the last 25 years the plasma industry has developed very well documented and effective procedures to collect and process plasma safely for the donors and the recipients.

We at CIPO will continue to work with Canadian Blood Services and Héma-Quebec to encourage blood and plasma donations and to make the most complete use of all components.

An average PI patient in Canada receives 30g – 40g of plasma product a month. It takes 1 to 2 hours for donors to fill a 0.85L bottle with plasma. 3 x 0.85L bottles plasma will make 10g bottle of plasma product. It takes between 9 and 12 people donating between 9 and 24 hours of time to collect enough plasma to treat one PID patient.

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HAE AOH
CANADA

October 6, 2017

Marie-Anik Gagné
Director / Plasma Policy
Health Canada
marie-anik.gagne@hc-sc.gc.ca

Dear Marie-Anik,

Thank you for your invitation to provide input to the Expert Panel on Immune Globulin Product Supply and Related Impacts in Canada. HAE (Hereditary Angioedema) Canada's President, Jacquie Badiou (president@haecanada.org), will be the contact person for our submission.

HAE Canada is a patient group that was formed in 2010 to work with physicians, nurses and other health care professionals to create a better life for those patients living with HAE and other related angioedema in Canada.

We are engaged with the International Patient Organization for C1 inhibitor deficiencies (HAEi) to further their mission of promoting cooperation, coordination and information sharing between HAE specialists and national patient associations in order to promote and facilitate the availability of effective diagnosis and management of HAE throughout the world. We also work closely with the physician group, CHAEN (Canadian Hereditary Angioedema Network), to advocate on behalf of Canadians with HAE. Together with CHAEN and other HAE international specialists, we co-authored the Canadian Hereditary Angioedema Guidelines in October 2014. The Guidelines provide recommendations for the management of patients in Canada with HAE and can be found on-line at: https://aacijournal.biomedcentral.com/articles/10.1186/1710-1492-10-50.

To get further input on HAE, please consider contacting CHAEN, The Canadian Hereditary Angioedema Network (http://chaen-rcah.ca/), an organization of physicians who treat and/or are interested in Hereditary Angioedema in Canada. You can reach their Executive Director, Peter Waite, at pwaite@chaen-rcah.ca.

HAE is a rare genetic disorder, affecting between 1 in 10,000 and 1 in 50,000 Canadians[1], which equates to approximately 880 patients in our country. HAE is characterized by episodes of swelling (edema attacks) in different areas of the skin or the internal organs. Edema of the mucous membranes of the larynx, nose or tongue is potentially life-threatening, as it can cause death by suffocation. Symptoms that are felt just before an attack in the throat may include difficulty swallowing, a hoarse voice, whistling or wheezing when breathing, a swollen tongue, cough, or shortness of breath. Patients who experience these unpredictable symptoms and suspect the start of such an attack are advised to seek emergency attention immediately.

Most patients experience their first attack during childhood or adolescence. The development of edema does not follow a typical pattern and therefore the site of the next episode of swelling cannot be predicted. The frequency, duration and severity of the edema vary considerably. Most HAE attacks occur spontaneously, but patients can often link specific situations that occur in their lives, such as stress, infections, trauma or dental procedures, to the development of edema. The disorder places extraordinary strain on patients, often restricting their ability to lead normal lives.

[1] (http://www.cslbehring.com/products/hereditary-angioedema-hae.htm)

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HAE AOH CANADA

Recently, HAE Canada asked our members to participate in a survey designed to gather data to assist in the process of obtaining new treatments in Canada. Out of our approximately 400 members, 124 responded. The results of this survey showed that that C1 inhibitor products are currently their primary treatment method. In Canada we need to reiterate that availability of blood plasma products are integral for patient treatment for overall wellness. Fortunately, treatment such as Berinert and Cinryze are covered under the provincial health plans under the Blood Coordination Program.

Currently, a new subcutaneous product is under consideration called HAEGARDA, by CSL Behring, for routine prophylaxis to prevent HAE attacks in both adult and adolescent patients. HAEGARDA is going to require 40-60 IU/kg twice a week for prophylaxis instead of 20 IU/kg when given IV. Further details can be found through the following link: http://www.cslbehring.com/newsroom/fda-grants-orphan-exclusivity-to-HAEGARDA. The abstract can also be viewed on the New England Journal of Medicine's website: http://www.nejm.org/doi/full/10.1056/NEJMoa1613627.

Shire is in the final stages of a clinical trial for Lanadelumab in Canada. If approved, Lanadelumab will significantly reduce HAE attacks when administered subcutaneously. To find more information please follow the link: http://www.genengnews.com/gen-news-highlights/shire-plans-lanadelumab-bla-submission-following-positive-phase-iii-hae-results/81254365.

Also, BioCryst is entering into Phase 3 of a clinical trial for BCX7353, a once-a-day oral treatment for HAE patients that will restore the normal phenotype of kallikrein inhibition. The goal for this new drug is to prevent angioedema attacks for those with HAE. More details can be found through the following link: http://www.biocryst.com/pipeline-product/next-generation-kallikrein-inhibitors-hae.

There are multiple reasons why it is particularly difficult to determine the future needs for C1 inhibitor products at this time. These reasons include:

- We do not currently have a registry to track product use in HAE patients, fortunately, plans are underway for an HAE registry that will include Canadians;
- HAE attacks are extremely unpredictable;
- Each patient requires treatment on-demand, STP (short term prophylaxis) or LTP (long term prophylaxis) at different times in their lives;
- It can unfortunately take up to eight years for a patient to be properly diagnosed with HAE, and as the number of properly diagnosed patients increases, so will the demand for plasma products.

In conclusion, it is important to emphasize the need for timely publicly funded access to treatments such as HAEGARDA and BCX7353 once they have been approved in Canada. Administration of the intravenous products can be difficult and painful due to poor vein access and requires more preparation time than taking subcutaneous or oral medications. Some patients require nurses in Day Treatment clinics to administer their prophylactic IV products. Having Subcutaneous and oral treatments in addition to intravenous treatments would address patient's needs more completely, lessen the need for visits to the hospitals for routine treatments and help in organizing and planning their lives. Only by ensuring universal access to all medications for HAE can we meet the critical needs of the patients and their families living with this disease. It is imperative for HAE patients to have full access to plasma products as treatments are essential in empowering and equipping patients to live healthy and productive lives. We appreciate the opportunity you have given to submit input to the panel.

HAE Canada on Paid Blood Plasma Donations

Toronto, March 20, 2013

HAE Canada shares the stated positions of the Canadian Blood Services[1] and the Canadian Hemophilia Society[2] that support the long-held practice of using plasma products that were sourced from paid blood donors in treatment of rare blood disorders.

It has been recognized that the demand for plasma products has exceeded the Canadian capacity of plasma collection for decades. In fact, most of the world's supply of fractionated plasma products comes from paid donors. 80% of the plasma needed to manufacture products used in Canada comes from the USA, where donors are very likely to be paid for their plasma donations. HAE Canada considers these products safe and essential.

Plasma derived products are life-saving therapies for a number of rare blood diseases that affect thousands of Canadians, including our members who live with hereditary angioedema (referred to as HAE). HAE is a rare blood disorder resulting from a deficiency in C1 esterase inhibitor. It is a chronic, potentially life- threatening illness that causes episodes of swelling commonly affecting the face, throat, abdomen, and extremities. If left untreated, an upper airway obstruction can prove fatal for HAE patients.

The majority of people with HAE have a defective gene that results in their body producing inadequate or non-functioning C1 Inhibitor – the blood protein that stops swelling. There is no cure for HAE yet. The efficacy of plasma-derived C1- Inhibitor as replacement therapy for acute attacks of HAE has been documented.
Soon, new prophylactic therapies may also be available in most provinces.
HAE Canada is a not-for-profit patient organization that provides education and support services for Canadian hereditary angioedema patients and their families.

For more information, contact HAE Canada at info@haecanada.org. Please visit the HAE Canada website[3] for further information about HAE and useful links.

Peter Waite, CAE
Executive Director

1. http://bloodservices.ca/CentreApps/Internet/UW_V502_MainEngine.nsf/9749ca80b75a038585256aa20060d703/6759ee5e17db02e385257b2d0065c052?OpenDocument

2. http://www.hemophilia.ca/files/Policy%20on%20Paid%20Plasma%20Donations%2029-05-2013.pdf

3. http://www.haecanada.org/understanding/useful-links/

Immunodeficiency Canada
Immunodéficience Canada

Patient Support, Education and Research for a Cure for Primary Immunodeficiency

Immunodeficiency Canada / Immunodéficience Canada
Charitable Registration # 87276 0897 RR0001

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Submission to the Expert Panel on Immune Globulin Product Supply and Related Impacts in Canada

Date: October 6, 2017

Name: Immunodeficiency Canada

Contact: Richard Thompson, CFRE
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Disease

Primary Immunodeficiency (PI) occurs when an infant is born with a defective or no immune system. Individuals are unable to create antibodies. Even a common cold can be fatal. It can affect any one from any culture at any time. Often there is no history in family members.

There are over 300 genetic defects and disorder of the immune system recog nized by the World Health Organization as a Primary Immunodeficiency.

These forms range widely in severity and symptoms.

On average one in every 1,200 individuals is affected by this disease and ear ly diagnosis and treatment are vital in saving lives. Population prevalence of diag aosed primary immunodeficiency disease in the United States disease. Boyle JM, Buckley RH. J Clin Immunology. 2007 Sept;27(5):497-502.

Incidents of PI in Canada

Approximately 29,000 Canadians suffer from a PI.

Base line surveys competed at the major health care centres across Canada indicate that 70% are undiagnosed. Jeffrey Model Foundation, Baseline Surveys, jmf.org

Immunoglobulin Replacement Therapy (IG) made from plasma is the only treatment available to replace missing antibodies.

One treatment contains the antibodies of thousands of individuals. *Looney RJ, Huggins J. Use of intravenous immunoglobulin (IVIG). Best Pract Res Clin Haematol. 2006;19(1):3–23. [PubMed]*

Over 750 individuals are on IG Therapy in Canada Jeffrey Model Foundation, Base line Surveys, jmf.org

IG Therapy is a life long treatment. You don't stop. It is this exposure to the great number of donor's antibodies that in fact protects an individual with Primary Immunodeficiency from illness.

Follow Immunodeficiency Canada on social media!

Projections

With a rate of one in 1,200 applied to newborns in Canada, (380,323 newborns in 2013) Stats Canada, there are 316 infants each year born with a PI.

As newborns and individuals affected by PI are better diagnosed, the number who are identified and will need IG Therapy is going to increase.

We estimate a 5 — 10% year increase in IG use.

Costs

All Immunoglobulin Replacement Therapy (IG) costs are covered by provincial health care when administered within the hospital/healthcare setting. For home therapy the cost of Immunoglobulin Replacement Therapy is covered, but not the equipment and supplies necessary to administer it. This creates a financial burden on the patient.

National Immunoglobulin Replacement Expert Committee Recommendations

These recommendations are listed on page three. A full paper on the recommendations are scheduled to be published December, 2017, in the LymphoSign Journal, The journal of inherited immune disorders, ISSN 2292-5937

NATIONAL IMMUNOGLOBULIN REPLACEMENT EXPERT COMMITTEE RECOMMENDATIONS

Management and Diagnosis

1. Children and adults with a suspected immunodeficiency (Table 1, 2) should be referred to an immunologist with experience in the field.

2. Suspected or confirmed cases of antibody deficiency should be evaluated by an immunologist with experience and expertise in the field of primary immunodeficiency ('expert' in PID).

3. Ideally, this should be carried out in an academic centre with a capability of performing specialized tests. Follow-up should be performed by a specialized team including physicians, nurses and allied health care providers.

4. Only 'experts' should be able to recommend initiation of replacement with IVIG or SCIG, change in dosing, switching preparation of modality of treatment.

5. Diagnosis of antibody deficiency should be confirmed by the following tests

A) Low serum IgG with or without a reduction of IgA and IgM
B) Abnormal antibody formation with or without a reduction in serum immunoglobulins (hypogammaglobulinemia/ dysgammglobulinemia).
C) Ability to sustain antibody levels in response to immunization.
D) Immunophenotyping including enumeration of memory and naive B and T cells.
E) In-vitro mitogenic responses.
F) Assessment of TRECs and TCR-Vb.
G) Genetic analysis

Replacement Therapy

6. IVIG is the most extensively studied and most commonly used Ig replacement therapy and recommended as a first line of therapy.

7. SCIG is used interchangeably with IVIG following the assumption that both modalities are comparable in preventing infections.

8. IVIG and SCIG deliver IgG differently resulting in different pharmacokinetic properties. An 'expert' should tailor the most suitable choice for each patient.

9. After a detailed description of benefits as well as challenges associated with IVIG or SCIG, patient preference should be taken into account.

10. Serum IgG trough levels should exceed 500 mg/dL (FDA standard) and should be kept in the normal range per age while optimizing clinical response.

11. These trough levels are usually achieved by administration of 400-600 mg/kg IVIG, which is sometime increased up to 900 mg/kg every 3-4 weeks.

12. SCIG dosing is usually 100-150 mg/kg per week.

Network of Rare Blood Disorder Organizations

Expert Panel on Immune Globulin Product Supply and Related Impacts in Canada
REQUEST FOR INPUT: PATIENT / PRODUCT USER GROUPS

Name of organization: Network of Rare Blood Disorder Organizations (NRBDO) / Réseau des Associations Vouées aux Troubles Sanguins Rares (RAVTSR)
Contact person: Jennifer van Gennip, NRBDO Administrator | info@nrbdo.ca

The NRBDO is a pan Canadian coalition of not-for-profit organizations representing people with rare blood disorders and/or people with a chronic condition who are recipients of blood or blood products or their alternatives.

Member groups:

- Answering TTP (Thrombotic Thrombocytopenic Purpura)*
- Canadian Association for Porphyria (CAP)
- Canadian Hemophilia Society (CHS)*
- Canadian Immunodeficiencies Patient Organization (CIPO)*
- Canadian Organization for Rare Disorders (CORD)
- Fanconi Canada
- HAE Canada (Hereditary Angioedema)*
- Sickle Cell Disease Association of Canada (SCDAC)
- Thalassemia Foundation of Canada (TCF)

*These member groups represent patients who rely on plasma-derived products. The individual submissions of these patient groups will provide the patient demographic information you are seeking.

The NRBDO has had a vested interest in the blood safety and supply in Canada for over a decade, from the perspective of patients who rely on these products to stay alive.

Products Used To Treat Conditions Represented By NRBDO Member Organizations

Disease	Treatment Product	Plasma Source
TTP (Thrombotic Thrombocytopenic Purpura)	Untreated Plasma	Unpaid donors
	Solvent detergent treated plasma	Paid donors in U.S.
Immunodeficiency	Immunoglulin products	Paid donors in U.S.
Hereditary angioedema	C1 esterase inhibitor	Paid donors in U.S.
A1 antiripsin deficiency	A1 antitripsin concentrate	Paid donors in U.S.
Clotting factor deficiencies		
Factor II, VII, X, XI, and XIII deficiencies	Plasma derived products	Paid donors in U.S.
Factor I deficiency	Plasma derived product	Unpaid donors
Factor V deficiency	Solvent detergent treated plasma	Paid donors in U.S.
von Willebrand disease	Humate	Unpaid donors
	Wilate	Paid donors in U.S.

Network of Rare Blood Disorder Organizations

Position related to the mandate of this panel:
It is the position of the NRBDO that with no evidence of safety risks, and no evidence of threats to the voluntary collection of blood, paid plasma can help with the global supply shortage, ensuring patients can access plasma products when they need them.

The donation of whole blood, collected by a not-for-profit blood establishment such as Canadian Blood Services (CBS) must remain voluntary and non-compensated.

However, plasma products are manufactured by for-profit multi-national corporations, and sold to the provinces and territories, just like any other drug. The manufacture and sale of plasma products is almost entirely a private, for-profit operation, with plasma being the main raw ingredient. To say that the compensated collection of this ingredient puts our public health care system in peril is a stretch at best, and fear-mongering at worst. Indeed, these products are supplied at no direct cost to patients by CBS and Héma Québec, which could be a model for the rest of our public health system.

Additional information or evidence related to the mandate of the Panel:
At the present time, thousands of Canadians with chronic hematologic and immune-system disorders rely on plasma-derived products to maintain their health and keep them alive; and most of the plasma used to manufacture of these products comes from paid donors in the United States.

Of the 30 plasma-derived products distributed by the Canadian Blood Services (CBS), only two are produced wholly from unpaid Canadian donors. Twenty-six are produced solely from plasma from paid donors in the U.S., and two (immune globulin and albumin) are produced from a combination of both sources. More than 80 percent of the plasma required for these two products is produced from compensated U.S. donors. We submit that paying Canadians is no more or less ethical than paying Americans, as we do today for most of the plasma-derived medicinal products used across Canada.

It is of note to our group that Canadian Blood Services (CBS) is not without some bias on this issue, and has changed its position on the impact of paid plasma collection on voluntary whole-blood donation:

- In 2012 CBS closed a plasma collection facility citing the declining demand for plasma for transfusion.[1]
- In 2016, referencing other countries that use paid models, such as the United States, Germany, the Czech Republic and Austria, CEO Dr. Graham Sher told Global News that "In those places, one has not seen the emergence of for-profit plasma industry have a negative impact on blood collection."[2]

[1] "Canadian Blood Services announces closure of Thunder Bay Plasma Centre." March 29, 2012. https://blood.ca/en/journalists/canadian-blood-services-announces-closure-thunder-bay-plasma-centre
[2] Wong, Julia. "Pay for Plasma: The economics behind paid and unpaid systems." Global News. https://globalnews.ca/news/2652186/pay-for-plasma-the-economics-behind-paid-and-unpaid-systems

Network of Rare Blood Disorder Organizations

- Now in 2017, with a decrease in demand for whole blood,[3] and an increase in demand for plasma-derived products,[4] CBS finds plasma to be an integral part of its business plan moving forward, and as their interests in plasma have changed, so has its position on the dangers of compensated plasma collection. The proposed business plan includes provinces and territories providing $855 million in additional funding over the next seven years to open 40 plasma collection centres in an attempt to raise Canada's self-sufficiency from 17% to 50%.[5]

While we have searched for this newly mentioned evidence about negative impacts of paid plasma collection on the voluntary whole-blood donation system, we have found none. What we have found however is that the USA is able to meet their needs for whole blood through a robust voluntary, not-for-profit donation system while simultaneously supplying 70% of the world's plasma supply through a paid collection system. It would appear that the two systems are able to function side by side.

As a Health Canada Round Table discussion on compensating plasma donors concluded: "No country in the world has been able to meet their need for plasma with a solely volunteer model."[6]

Therefore, the NRBDO agrees with the findings of Kretschmer et al who concluded, "All measures improving the supply of safe blood, including monetary compensation, should be objectively discussed without prejudice."[7]

The NRBDO is committed to ensuring the patient voice is heard, and working with governments, CBS and H-Q to protect the safety and availability of blood products in Canada. We thank you for the opportunity to submit input to the panel.

[3] Wald, Matthew. "Blood Industry Shrinks as Transfusions Decline." New York Times. https://www.nytimes.com/2014/08/23/business/blood-industry-hurt-by-surplus.html?mcubz=0
[4] "Sales of Plasma Protein Therapeutics to Rise in Response to Increasing Demand for Immunoglobulin, says TMR." July 19, 2016. http://www.prnewswire.com/news-releases/sales-of-plasma-protein-therapeutics-to-rise-in-response-to-increasing-demand-for-immunoglobulin-says-tmr-587444041.html
[5] Grant, Kelly. "Blood agency seeking $855-million in funding to boost plasma supply, document reveals." The Globe and Mail. https://beta.theglobeandmail.com/news/national/blood-agency-seeking-$55-million-in-funding-to-boost-plasma-supply-document-reveals/article35980339/?ref=http://www.theglobeandmail.com&.
[6] "Round Table Discussion on Payment of Plasma Donors in Canada – Summary Report." April 10, 2013. https://www.canada.ca/en/health-canada/services/drugs-health-products/public-involvement-consultations/biologics-radiopharmaceuticals-genetic-therapies/round-table-discussion-payment-plasma-donors-canada-summary-report.html
[7] Kretschmer V, Weippert-Kretschmer M, Slonka J, Karger R, Zeiler T. Perspectives of paid whole and plasma donation. Developmental Biology 2005;120:101-11. https://www.ncbi.nlm.nih.gov/pubmed/16050162

APPENDIX E

HEALTH CARE PROVIDER ORGANIZATIONS

METHODOLOGY

- Thirty health care provider organizations were invited to submit written input on issues relevant to the Expert Panel on Immune Globulin Product Supply and Related Impacts in Canada (see List 1). Three organizations responded in February 2018: Canadian Rheumatology Association (CRA); Canadian Society of Allergy and Clinical Immunology (CSACI); and Ontario Regional Blood Coordinating Network (ORBCoN).
- Invitations were sent January 12, 2018 to select Health Care Groups to inform them of the work of the Expert Panel on Immune Globulin Product Supply and Related Impacts in Canada (the Panel), to request their input on the issue, and to invite them to participate in a teleconference hosted by the Panel's Chair and Deputy Chair.
- Invitations were sent to organizations representing providers of immune globulins and representing expertise in other areas of plasma products.
- To help focus their answers on issues of most interest to the Panel, and to facilitate our review of their submissions, groups were asked to respond to questions in their submission (see List 2).
- Submissions were not to exceed three pages in length, and were to be sent electronically by February 5, 2018. Staff followed up the first week of February to confirm that organizations had received the invitation and again the second week of February with organizations that had yet to respond.

List 1: Identified health care provider organizations and received submissions

Association des allergologues et immunologues du Québec
Association des chargés de sécurité transfusionnelle
Association des médecins microbiologistes infectiologues du Québec
Association des neurologues du Québec
Association des patients immunodéficients du Québec (APIQ)
Association of Hemophilia Clinic Directors of Canada (AHCDC)

Association of Medical Microbiology and Infectious Disease Canada
Atlantic Blood Utilization Strategy (ABUS)
Canadian Association of Emergency Physicians
Canadian Association of General Surgeons
Canadian Association of Neuroscience
Canadian Association of Paediatric Health Centres
Canadian Association of Pediatric Surgeons
Canadian Association of Thoracic Surgery
Canadian Critical Care Society
Canadian Hematology Society
Canadian Neurological Society
Canadian Paediatric Society
Canadian Medical Association
Canadian Rheumatology Association*
Canadian Society for Vascular Surgery
Canadian Society of Allergy and Clinical Immunology*
The Canadian Medical Association forwarded the Panel's request to these groups:
Canadian Society of Cardiac Surgeons
Canadian Society of Colon and Rectal Surgeons
Canadian Society of Otolaryngology Head and Neck Surgery
Canadian Society of Plastic Surgeons
Nova Scotia Provincial Blood Coordinating Program
Ontario Regional Blood Coordinating Network (ORBCoN)*
Transfusion Medicine Advisory Group (TMAG)
Trauma Association of Canada

*Groups highlighted responded

List 2: Questions

1. Please identify the name of your organization and provide the name/email of the contact person for the submission.
2. Please briefly describe who your organization represents, how your mandate relates to the plasma product supply, and the interest of your organization and/or its members in these issues.
3. If applicable, please provide any research your organization has conducted (e.g., population surveys) or published reports that summarize relevant research, data, or prescribing practices relevant to the Panel mandate. If possible, please attach or provide a link to this information below – your work will be shared with the Panel as part of their review of the topic. Please include a brief description of your research methods if available.
4. If applicable, please provide any formal position or policy statement that has been developed by your organization related to the mandate of the Panel (this may include published editorial, opinion pieces, utilization management guidelines). If such documents exist, please attach or paste below, specifying the source and date.
    - If not stated explicitly in the statement, please explain the rationale and evidence on which it was based. This might include input from membership of your organizations, the public, scientific evidence or public policy documentation behind your position, if available.
5. Please provide succinctly any additional information or evidence related to the mandate of the Panel that you wish to share with the members of the Panel.

Expert Panel on Immune Globulin Product Supply and Related Impacts in Canada
REQUEST FOR INPUT: HEALTHCARE PROFESSIONAL GROUPS

1. **Please identify the name of your organization and provide the name/email of the contact person for the submission.**

Canadian Rheumatology Association (CRA) is the national professional association for Canadian rheumatologists.
President: Dr. Joanne Homik; Chief Executive Officer: Dr. Ahmad M Zbib MD CPHIMS-CA, azbib@rheum.ca; Therapeutic committee Chair: Dr. Mary-Ann Fitzcharles, mfitzcharles@sympatico.ca;
Canadian Rheumatology Association, 12-16715 Yonge Street, Suite 244, Newmarket, Ontario, L3X 1X4. t: 905-952-0698, f: 905-952-0708, e: info@rheum.ca
For future correspondence on this issue, contact Ahmad Zbib (azbib@rheum.ca).

2. **Please briefly describe who your organization represents, how your mandate relates to the plasma product supply, and the interest of your organization and/or its members in these issues.**

The Canadian Rheumatology Association represents health care professionals caring for patients with rheumatic diseases across Canada. The membership comprises 572 health care professionals, most of whom are specialists in adult or childhood rheumatology as well as trainees entering the field of rheumatology. The mission of the Canadian Rheumatology Association is to represent Canadian Rheumatologists and promote the pursuit of excellence in arthritis and rheumatic disease care, education and research. Key areas of interest and activities of the CRA include supporting best practices, through development and dissemination of treatment guidelines, position papers and consensus statements and maintaining an awareness of the needs related to therapies for rheumatic diseases. The CRA is also alert to issues pertaining to supply of medicines and access to treatments and notifies the membership regarding specific medication-related issues. Other than for the management of Kawasaki's disease, a childhood vasculitis, IVIG treatment is mostly considered an extraordinary treatment that may be used to treat a variety of rheumatic conditions that are either poorly responsive to conventional therapy or in life threatening conditions. Other than for Kawasaki's disease, IVIG is generally not considered first line treatment for any condition. IVIG treatments are most commonly administered in a tertiary care setting.

3. **If applicable, please provide any research your organization has conducted (e.g., population surveys) or published reports that summarize relevant research, data, or prescribing practices relevant to the Panel mandate. If possible, please attach or provide a link to this information below – your work will be shared with the Panel as part of their review of the topic. Please include a brief description of your research methods if available.**

The CRA as an organization does not specifically conduct research. However the CRA provides important research funding via a peer reviewed process to support research of the rheumatic diseases in Canada. Grants for rheumatic disease research include those for basic science and preclinical study as well as clinical research. The CRA has been an important support for rheumatic disease researchers in Canada since its inception in 1936. Another important function of the CRA is to support the development of guidelines for the diagnosis and management of rheumatic diseases that are pertinent to the Canadian

patient population. Recent guidelines include those addressing rheumatoid arthritis, systemic lupus erythematosis, vasculitis and use of medical cannabis. Specifically pertaining to IVIG, a North American consensus with prominent Canadian rheumatologist representation has developed a recommended treatment plan for juvenile dermatomyositis. In the setting of persistent skin rash there is a recommendation to use IVIG therapy.

> ***Childhood Arthritis and Rheumatology Research Alliance Consensus Clinical Treatment Plans for Juvenile Dermatomyositis with Persistent Skin Rash***. Huber AM, et al and Juvenile Dermatomyositis Research Committee of the Childhood Arthritis and Rheumatology Research Alliance. J Rheumatol. 2017 Jan;44(1):110-116.

Contributions to the peer reviewed literature by Canadian rheumatologists regarding use of IVIG in various rheumatic diseases are as follows:

a. Kawasaki disease

> ***Aspirin Dose and Prevention of Coronary Abnormalities in Kawasaki Disease.*** Dallaire F, Fortier- Morissette Z, Blais S, Dhanrajani A, Basodan D, Renaud C, Mathew M, De Souza AM, Dionne A, Blanchard J, Saulnier H, Kaspy K, Rached-d'Astous S, Dahdah N, McCrindle BW, Human DG, **Scuccimarri** R. Pediatrics. 2017 Jun;139(6).
> ***Kawasaki disease.*** **Scuccimarri R**. Pediatr Clin North Am. 2012 Apr;59(2):425-45.
> ***Hemolytic anemia following intravenous immunoglobulin therapy in patients treated for Kawasaki disease: a report of 4 cases***. Berard R, Whittemore B, **Scuccimarri R**. Pediatr Rheumatol Online J. 2012 Apr 16;10(1):10.

b. Juvenile dermatomyositis

> ***Childhood Arthritis and Rheumatology Research Alliance Consensus Clinical Treatment Plans for Juvenile Dermatomyositis with Persistent Skin Rash.*** Huber AM, Kim S, Reed AM, Carrasco R, **Feldman BM**, Hong SD, Kahn P, Rahimi H, Robinson AB, Vehe RK, Weiss JE, Spencer C; Juvenile Dermatomyositis Research Committee of the Childhood Arthritis and Rheumatology Research Alliance. J Rheumatol. 2017 Jan;44(1):110-116.
> ***Efficacy of intravenous Ig therapy in juvenile dermatomyositis.*** Lam CG, Manlhiot C, Pullenayegum EM, **Feldman BM**. Ann Rheum Dis. 2011 Dec;70(12):2089-94.
> **Juvenile dermatomyositis.** Batthish M, Feldman BM.Curr Rheumatol Rep. 2011 Jun;13(3):216-24.
> ***Treatment approaches to juvenile dermatomyositis (JDM) across North America: The Childhood Arthritis and Rheumatology Research Alliance (CARRA) JDM Treatment Survey.*** Stringer E, Bohnsack J, Bowyer SL, Griffin TA, **Huber AM**, Lang B, Lindsley CB, Ota S, Pilkington C, Reed AM, **Scuccimarri R, Feldman BM**. J Rheumatol. 2010 Sep;37(9):1953-61.
> ***Juvenile dermatomyositis and other idiopathic inflammatory myopathies of childhood.*** **Feldman BM**, Rider LG, Reed AM, Pachman LM. Lancet. 2008 Jun 28;371(9631):2201-12.
> ***Safety of intravenous immunoglobulin in the treatment of juvenile dermatomyositis: adverse reactions are associated with immunoglobulin A content.*** Manlhiot C, Tyrrell PN, Liang L, Atkinson AR, Lau W, **Feldman BM**. Pediatrics. 2008 Mar;121(3):e626-30.

c. Adult vasculitis

> ***Mononeuritis multiplex predicts the need for immunosuppressive or immunomodulatory drugs for EGPA, PAN and MPA patients without poor-prognosis factors.*** Samson M, Puéchal X,

Devilliers H, Ribi C, Cohen P, Bienvenu B, Terrier B, **Pagnoux C**, Mouthon L, Guillevin L; French Vasculitis Study Group (FVSG). Autoimmun Rev. 2014 Sep;13(9):945-53.
[Pregnancy and vasculitides]. **Pagnoux C**. Presse Med. 2008 Nov;37(11):1657-65.
[Treatment of systemic vasculitides]. Guillevin L, Pagnoux C. Rev Prat. 2008 Mar 15;58(5):541-4. Review. French.

Treatment of refractory and/or severe ANCA-associated systemic necrotizing vasculitides. Guillevin L, **Pagnoux C**. Isr Med Assoc J. 2008 Jan;10(1):89-91. Review.
Intravenous immunoglobulins for relapses of systemic vasculitides associated with antineutrophil cytoplasmic autoantibodies: results of a multicenter, prospective, open-label study of twenty-two patients. Martinez V, Cohen P, **Pagnoux C**, Vinzio S, Mahr A, Mouthon L, Sailler L, Delaunay C, Sadoun A, Guillevin L; French Vasculitis Study Group. Arthritis Rheum. 2008 Jan;58(1):308-17.
Therapeutic strategies for systemic necrotizing vasculitides. Guillevin L, **Pagnoux C**. Allergol Int. 2007 Jun;56(2):105-11. Epub 2007 May 1. Review.
Indications for biotherapy in systemic vasculitides. Guillevin L, **Pagnoux C**, Guilpain P, Bienvenu B, Martinez V, Mouthon L. Clin Rev Allergy Immunol. 2007 Feb;32(1):85-96. Review.
[Treatment of ANCA-associated vascularitides]. Guillevin L, Pagnoux C. Presse Med. 2007 May;36(5 Pt 2):922-7.

d. Adult idiopathic inflammatory myopathies

Critical review of the role of intravenous immunoglobulins in idiopathic inflammatory myopathies. Anh-Tu Hoa S, **Hudson M**. Semin Arthritis Rheum. 2017 Feb;46(4):488-508.

4. **If applicable, please provide any formal position or policy statement that has been developed by your organization related to the mandate of the Panel (this may include published editorial, opinion pieces, utilization management guidelines). If such documents exist, please attach or paste below, specifying the source and date.**

To date the CRA has not developed any guidelines or position statement in regard to the use of IVIG in rheumatic diseases. However Canadian guidelines for the management of vasculitis have recently been published and is endorsed by the CRA. The 2 publications are listed below and incorporate a recommendation for use of IVIG in in the section on additional and experimental therapies, section 8 of the J Rheumatology publication.

CanVasc Recommendations for the Management of Antineutrophil Cytoplasm Antibody-associated Vasculitides. McGeoch L, Twilt M, Famorca L, Bakowsky V, Barra L, Benseler SM, Cabral DA, Carette S, Cox GP, Dhindsa N, Dipchand CS, Fifi-Mah A, Goulet M, Khalidi N, Khraishi MM, Liang P, Milman N, Pineau CA, Reich HN, Samadi N, Shojania K, Taylor-Gjevre R, Towheed TE, Trudeau J, Walsh M, Yacyshyn E, Pagnoux C; Canadian Vasculitis Research Network.
J Rheumatol. 2016 Jan;43(1):97-120.

CanVasc recommendations for the management of antineutrophil cytoplasm antibody (ANCA)-associated vasculitides - Executive summary. McGeoch L, Twilt M, Famorca L, Bakowsky V, Barra L, Benseler S, Cabral DA, Carette S, Cox GP, Dhindsa N, Dipchand C, Fifi-Mah A, Goulet M, Khalidi N, Khraishi MM, Liang P, Milman N, Pineau CA, Reich H, Samadi N, Shojania K, Taylor-Gjevre R, Towheed TE, Trudeau J, Walsh M, Yacyshyn E, Pagnoux C; Canadian Vasculitis research network (CanVasc).
Can J Kidney Health Dis. 2015 Nov 9;2:43.

5. **Please provide succinctly any additional information or evidence related to the mandate of the Panel that you wish to share with the members of the Panel.**

There are a number of rheumatic disease conditions where IVIG has become an important treatment component.

a. Kawasaki Disease. This is the most common form of vasculitis in childhood and can result in long term consequences of coronary artery aneurysms. IVIG in high doses is highly effective in reducing the development of aneurysms in children.
b. Childhood dermatomyositis, especially for treatment resistant skin disease.
c. Systemic onset Juvenile inflammatory arthritis that is poorly responsive to conventional treatments.
d. Treatment resistant vasculitis collectively known as ANCA-associated vasculitis including granulomatosis with polyangiitis, microscopic polyangiits, and eosinophilic granulomatosis with polyangiitis. Although these conditions generally respond to conventional therapies with corticosteroids, immunonosuppressive treatments or rituximab, IVIG may be considered in patients resistant to treatment, or when conventional therapies are contraindicated.
e. Treatment resistant immunological disease including systemic lupus erythematosis, (especially lupus-associated immune thrombocytopenia, lupus-associated autoimmune haemolytic anaemia, chronic inflammatory demyelinating polyneuropathy, and lupus-associated Guillan-Barre syndrome), and catastrophic antiphospholipid syndrome and ischaemic stroke (although use in this setting in pregnancy is controversial). IVIG is often used as a last-resort treatment for organ specific complications of systemic lupus erythematosis
f. Treatment resistant adult idiopathic inflammatory myopathies, with a multicenter Canadian study recently initiated.

Key members of the Canadian rheumatology community who have contributed to the knowledge of IVIG in rheumatology practice are Dr. Brian Feldman, Univ of Toronto, Dr. Rosi Scuccimarri, McGill University, Dr. Christian Pagnoux, Univ of Toronto, Dr. Marie Hudson McGill University

CANADIAN SOCIETY OF ALLERGY AND CLINICAL IMMUNOLOGY

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VIA EMAIL: robyn.cummings@canada.ca

February 5, 2018

Robyn Cummings
Research and Policy Analyst
Plasma Secretariat
Health Programs and Strategic Initiatives Directorate
Strategic Policy Branch
Health Canada

Dear Ms. Cummings,

Further to your email to the CMA, please find below the response from the Canadian Society of Allergy and Clinical Immunology (CSACI).

1. *Please identify the name of your organization and provide the name/email of the contact person for the submission.*

   The name of our organization is the Canadian Society of Allergy and Clinical Immunology (CSACI). The contact person is Dr. David Fischer, the CSACI President and his email is: davidafischer@rocketmail.com

2. *Please briefly describe who your organization represents, how your mandate relates to the plasma product supply, and the interest of your organization and/or its members in these issues.*

   Our organization represents the close to 200 Allergists and Clinical Immunologists of Canada. Immunology specialists write orders for, and supervise the provision of IVIg and SCIg to the vast majority of Canadians who suffer from Immunodeficiency. We wish to ensure that our patients will continue to be able to obtain their IVIg and SCIg therapies without interruption. We are called upon to help our patients decide which form of therapy (IVIg vs SCIg) is right for them and to deal with any adverse reactions related to the therapies, so having a diverse portfolio of Ig products available now and in the future, are needed to meet the needs of our patients.

3. *If applicable, please provide any research your organization has conducted (e.g., population surveys) or published reports that summarize relevant research, data, or prescribing practices relevant to the Panel mandate. If possible, please attach or provide a link to this information below – your work will be shared with the Panel as part of their review of the topic. Please include a brief description of your research methods if available.*

   Dr. Christine McCusker developed the first SCIg program for SCIg in Canada and has conducted quality of life studies in this area (see Additional References). She has also been a lead site investigator for clinical trials related to the use of SCIg in previously untreated patients with primary immunodeficiency. She is also the principle investigator for C-PRIMES a pan Canadian registry for patients with primary immunodeficiency

   She and Dr. Bruce Mazer have published a number of studies improving our knowledge on the safety and proper provision of immunoglobulins (see Additional References).

.../2

4. *If applicable, please provide any formal position or policy statement that has been developed by your organization related to the mandate of the Panel (this may include published editorial, opinion pieces, utilization management guidelines). If such documents exist, please attach or paste below, specifying the source and date.*
   - *If not stated explicitly in the statement, please explain the rationale and evidence on which it was based. This might include input from membership of your organizations, the public, scientific evidence or public policy documentation behind your position, if available.*

This a copy of the 'National Immunoglobulin replacement Expert Committee recommendations'. They appeared in the Lymphosign Journal Volume 4, 2017 pages 117-118. This article was made available by Immunodeficiency Canada

5. *Please provide succinctly any additional information or evidence related to the mandate of the Panel that you wish to share with the members of the Panel.*

With respect to having available differing immunoglobulin products, a recent study appeared in *Allergy, Asthma and Clinical Immunology* highlighting why having more diverse products available can help especially if there are manufacturing issues:

The study examined the constituents of SCIg product known as Subcuvia. In four patients, there were reports of delayed hypersensitivity reactions and later anaphylaxis to pollen and peanut exposure in patients on SCIg therapy. Analysis of the SCIg lot demonstrated significant amount of allergen specific IgE in the SCIg product. Of note, similar analysis of product from another company did not demonstrate allergen specific IgE and the implicated patients were successfully transitioned to the IgE poor product.

Zdziarski P, Gamian A, Majda J, Korzeniowska-Kowal A. Passive blood anaphylaxis: subcutaneous immunoglobulins are a cause of ongoing passive anaphylactic reaction. *Allergy, Asthma, and Clinical Immunology : Official Journal of the Canadian Society of Allergy and Clinical Immunology*. 2017;13:41. doi:10.1186/s13223-017-0213-x.

Additional References

IVIg/SCIg publications from Drs. McCusker and Mazer:

1. Update on the use of immunoglobulin in human disease: A review of evidence.
Perez EE, Orange JS, Bonilla F, Chinen J, Chinn IK, Dorsey M, El-Gamal Y, Harville TO, Hossny E, **Mazer** B, Nelson R, Secord E, Jordan SC, Stiehm ER, Vo AA, Ballow M.
J Allergy Clin Immunol. 2017 Mar;139(3S):S1-S46. doi: 10.1016/j.jaci.2016.09.023. Epub 2016 Dec 29.
Review

2. Efficacy and safety of subcutaneous vivaglobin® replacement therapy in previously untreated patients with primary immunodeficiency: a prospective, multicenter study.
Borte M, Quinti I, Soresina A, Fernández-Cruz E, Ritchie B, Schmidt DS, **McCusker** C.
J Clin Immunol. 2011 Dec;31(6):952-61. doi: 10.1007/s10875-011-9588-5. Epub 2011 Sep 20

The use of immunoglobulin therapy for patients with primary immune deficiency: an evidence-based practice guideline.
Transfus Med Rev. 2010 Jan;24 Suppl 1:S28-50. doi: 10.1016/j.tmrv.2009.09.011. Shehata N et al.

3. Consistency of protective antibody levels across lots of intravenous immunoglobulin preparations.
Lejtenyi D, **Mazer** B.
J Allergy Clin Immunol. 2008 Jan;121(1):254-5. doi: 10.1016/j.jaci.2007.11.001.

4. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology.

Orange JS, Hossny EM, Weiler CR, Ballow M, Berger M, Bonilla FA, Buckley R, Chinen J, El-Gamal Y, **Mazer** BD, Nelson RP Jr, Patel DD, Secord E, Sorensen RU, Wasserman RL, Cunningham-Rundles C; Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol. 2006 Apr;117(4 Suppl):S525-53. Review. Erratum in: J Allergy Clin Immunol. 2006 Jun;117(6):1483.

RESPONSE FROM Ontario Regional Blood Coordinating Network

Expert Panel on Immune Globulin Product Supply and Related Impacts in Canada
REQUEST FOR INPUT: HEALTHCARE PROFESSIONAL GROUPS

INPUT REQUESTED:

1. Please identify the name of your organization and provide the name/email of the contact person for the submission.

The Ontario Regional Blood Coordinating Network (ORBCoN) is a program funded by the Ontario Ministry of Health and Long-Term Care (MOHLTC), Provincial Agencies Trillium Gift of Life/Blood and Specialized Programs (PATB). ORBCoN was launched in 2006 to facilitate a comprehensive and integrated approach to blood utilization management in the province.

Contact name: Wendy Owens wowens@toh.ca

2. Please briefly describe who your organization represents, how your mandate relates to the plasma product supply, and the interest of your organization and/or its members in these issues.

ORBCoN is situated in three sponsor organizations – The Ottawa Hospital, Sunnybrook Health Sciences Centre and McMaster University in order to provide coverage for the large geographical area of Ontario. ORBCoN is staffed by ten individuals that provide expertise in Transfusion Medicine (both technical and clinical) as well as two support staff.

ORBCoN was put in place to engage hospital personnel and provide province-wide communication and educational resources relating to the appropriate use and management of blood components and blood products, justified by evidence based decision making, in order to maintain the blood system in a sustainable way while improving patient transfusion safety. Through the regional model, ORBCoN is able to provide a link between smaller, more remote hospitals and larger facilities to provide standardized communication, education and access to technical and clinical expertise.

One of the first priorities given to ORBCoN was to investigate the utilization of Intravenous Immune Globulin (IVIG) in Ontario due to the continuing increase in demand and concerns over the ability of the MOHLTC to sustain support for the growing cost of this product. Since 2006, ORBCoN has been involved in initiatives to improve the oversight of IVIG utilization. Working under the guidance of the Ontario Immune Globulin Advisory Panel (IGAP), several resources have been developed and provided to hospitals in the province in order to standardize the process for prescribing, ordering and calculating the dose of this product. As there is no single data collection mechanism within the province of Ontario, initially little was known at a provincial level about the use of this product. Through audits and recently a screening pilot for neurological indications, more information has been gained. However, Ontario is still seeking ways to further improve understanding of the utilization of immune globulin (IG) and the ever increasing demand for it.

In 2012, the Ontario MOHLTC released a strategy document in an effort to standardize utilization of IVIG. To help support hospitals in their implementation of this strategy, and to standardize management of the product, ORBCoN facilitated the development and distribution of a toolkit containing guidelines on utilization and infusion of IVIG. The primary objective of all of the initiatives implemented in the province is to ensure that IG is being used appropriately to ensure that patients that depend on it will continue to have access to it.

Feb 5, 2018

3. If applicable, please provide any research your organization has conducted (e.g., population surveys) or published reports that summarize relevant research, data, or prescribing practices relevant to the Panel mandate. If possible, please attach or provide a link to this information below – your work will be shared with the Panel as part of their review of the topic. Please include a brief description of your research methods if available.

The documents mentioned above in point 2 may be found on the transfusionontario.org website through this link http://transfusionontario.org/en/documents/?cat=ivig
Data and methods are included within the relevant documents.

4. If applicable, please provide any formal position or policy statement that has been developed by your organization related to the mandate of the Panel (this may include published editorial, opinion pieces, utilization management guidelines). If such documents exist, please attach or paste below, specifying the source and date.
   - If not stated explicitly in the statement, please explain the rationale and evidence on which it was based. This might include input from membership of your organizations, the public, scientific evidence or public policy documentation behind your position, if available.

The Ontario IVIG Strategy document can be found through the link above.

Feb 5, 2018

APPENDIX F

STAKEHOLDER GROUPS

METHODOLOGY

- Eleven stakeholder organizations were invited to submit written input on issues relevant to the Expert Panel on Immune Globulin Product Supply and Related Impacts in Canada (see List 1). Seven organizations responded in October 2017: Canadian Health Coalition (CHC); Blood Watch; Canadian Labour Congress (CLC); Canadian Federation of Nurses Unions (CFNU); Council of Canadians (CoC); Canadian Union of Public Employees (CUPE), and New Brunswick Health Coalition (NBHC).
- Invitations were sent September 27, 2017 to selected Stakeholder Groups to inform them of the work of the Expert Panel on Immune Globulin Product Supply and Related Impacts in Canada (the Panel), to request their input on the issue, and to invite them to participate in a teleconference hosted by the Panel's Chair and Deputy Chair.
- Invitations were sent to national / umbrella organizations that have taken a stand on issues related to availability and supply of various plasma products, selected based on their documented recent engagement related to plasma donation in Canada (identified primarily from the Blood Watch web page "Who's against paid plasma?").
- Organizations with multiple members or chapters that share a common interest and position were encouraged to send joint submissions.
- To help focus their answers on issues of most interest to the Panel, and to facilitate our review of their submissions, groups were asked to respond to the following questions in their submission (see List 2).
- Submissions were not to exceed three pages in length, and were to be sent electronically by October 6, 2017 Staff followed up the first week of October to confirm that organizations had received the invitation and again the week of October 10, 2017 with organizations that had yet to respond.

List 1: Identified stakeholder groups and received submissions

Blood Watch*
Canadian Doctors for Medicare (CDM)
Canadian Federation of Nurses Unions (CFNU)*
Canadian Health Coalition (CHC)*
Canadian Labour Congress (CLC)*
Canadian Nurses Association (CNA)
Canadian Union of Public Employees (CUPE)*
Council of Canadians*
National Union of Public and General Employees (NUPGE)
New Brunswick Health Coalition (NBHC)*
Unifor

*Group submitted a response

List 2: Questions

1. Please identify the name of your organization and provide the name/email of the contact person for the submission.

2. Please briefly describe who your organization represents, how your mandate relates to the plasma product supply, and the interest of your organization and/or its members in these issues.

3. Please provide any research your organization has conducted (e.g.population surveys) or published reports that summarize relevant research, laws, data, or practices relevant to the Panel mandate. If possible, please attach or provide a link to this information below – your work will be shared with the Panel as part of their review of the topic. Please include a brief description of your research methods if available.

4. Please provide any formal position or policy statement that has been developed by your organization related to the mandate of the Panel (this may include published editorial or opinion pieces). If such documents exist, please attach or paste below, specifying the source and date.

    + If not stated explicitly in the statement, please explain the rationale and evidence on which it was based. This might include input from membership of your organizations, the public, scientific evidence or public policy documentation behind your position, if available.

5. Please provide succinctly any additional information or evidence related to the mandate of the Panel that you wish to share with the members of the Panel.

BloodWatch.org
2140A Queen Street East, PO Box 51523,
Toronto, ON M4E 3V7, Canada, 647.272.7381
info@BloodWatch.org www.BloodWatch.org

October 5, 2017

HEALTH CANADA SUBMISSION TO EXPERT PANEL: Expert Panel On IG Product Supply & Related Impacts In Canada

Contact: Executive Director / Kat Lanteigne / 647/272.7381 / info@bloodwatch.org

BloodWatch is a not-for-profit organization advocating for a safe, voluntary, public blood system in Canada. We are committed to upholding Justice Horace Krever's landmark inquiry and his recommendations. BloodWatch represents tainted blood survivors, their family members and ongoing users of plasma-derived medications across Canada.

BloodWatch is actively advocating for each province in Canada and for the Federal Government to implement a version of The Voluntary Blood Donations Act, which was passed in Ontario in a unanimous vote in 2014 and in Alberta in March of 2017. The legislation protects the public blood system and bans the private sale of blood and plasma; in doing so, the new law upholds Justice Krever's recommendations, protects the *integrity* of Canada's national integrated voluntary blood system and secures plasma supply for Canadian patients.

BloodWatch supports Canadian Blood Services (CBS) as our only national blood operator. As an advocacy organization, watchdog and patient group we do not accept or solicit funds from the private for-profit plasma industry. BloodWatch is a non-partisan organization that holds official stakeholder status with Canadian Blood Services.

Plasma, just like whole blood, is a public resource that must be safeguarded for Canadians. Long-term security of the plasma supply for Ig can only be achieved through increased plasma collection by the publicly funded and publicly accountable not-for-profit blood system operated by Canadian Blood Services.

January 24, 2017 – Canadian Blood Services

BloodWatch...

We are extremely dismayed that Health Canada has not halted the licensing process for Canadian Plasma Resources (CPR). Canadian Blood Services has directly cited a risk to the security of supply in Canada and made it clear that, as the public national blood operator, it is their role to fulfill the need for increased plasma demand. While we appreciate renewed efforts for a public consultation, it must be recognized that there is a major breech of protocol in effect. In our view, public funds should be directed to support CBS and this discussion should be focused on how to retain a new generation of plasma donors for our voluntary system. Moreover, processes and procedures at Health Canada on how public blood policy decisions are made are in need of major reform.

The reality is that Health Canada, the Saskatchewan and New Brunswick Governments have made strident efforts to directly undermine our voluntary blood system by allowing a parallel private collector to proliferate in Canada. Decisions relating to our Canadian blood system are meant to take place in an open, transparent and honest manner by all parties responsible. The Federal Government is a signatory to the MOU that created CBS, as such; Health Canada has a fiduciary duty to act in the best interests of Canadians. Engagement with CPR, the granting of their license in Saskatchewan and in New Brunswick was neither honest nor transparent denoting a major breech of public trust.

We have attached the full business plan of CPR, which has been obtained via an FOI request, to demonstrate how vast CPR's plans are. CBS board chair, Leah Hollins, has assured BloodWatch, in writing, that CBS will not buy any plasma CPR collects: we would like to make it very clear that we acknowledge this assurance from CBS to include the purchasing of Canadian plasma product from Biotest AG whom CPR is partnered with.

We have attached our BloodWatch presentation, CBS' presentation to the IPFA panel on security of supply and ask that you visit our website at BloodWatch.org, where we have included a detailed FAQ on this issue. Below are a few highlights of common misconceptions on the plasma file.

- **"Paid-plasma coexists in other countries and has no impact on voluntary systems."** This is a false statement and one that should have never been perpetuated by Health Ministries, Health Canada or CBS. The **European Blood Alliance**, of which CBS is an international member, issued a ground-breaking report in 2013 detailing the impact of paid-plasma in both Germany and Austria and named the risks of for-profit plasma companies. http://www.europeanbloodalliance.eu/
- **"80% of plasma-derived medications come from the US where they source plasma from paid-donors so we should allow it here."** CBS should never have allowed Canadian patients to become so reliant on foreign sourced plasma. While other countries such as Australia, The Netherlands and New Zealand began to take steps to increase

collection and drastically reduce reliance of foreign sourced plasma. CBS did not take action as the demand increased. CBS are now implementing a long-overdue domestic strategy for plasma collection as they have recognized that political instability, a new blood-borne virus, or a disruption in the market could all impact CBS' ability to continue to rely on foreign sourced paid-plasma.
https://www.youtube.com/watch?v=AF9X915zPLNQ /
https://www.theatlantic.com/health/archive/2014/05/blood-money-the-twisted-business-of-donating-plasma/362012/
http://www.who.int/bloodsafety/Expert_Consensus_Statement_Self-Sufficiency.pdf

- **"Paid-plasma is not a safety issue."** While it is recognized, as it was by Justice Krever in his report, that advanced technology inactivates known pathogens, it is widely understood that paid-plasma has a higher infection rate and modern day technology does not work for non-enveloped viruses. In addition, the security of supply, supply management, donor care, and access to supply through a voluntary system *are all safety issues*. We challenge the limited perspective of Health Canada that only the "end-product" of plasma-derived medication matters.
- **"There is a facility in Winnipeg that pays people to sell their plasma, this is a perfect example of why we should allow paid-plasma in Canada."** The facility in Winnipeg, Cangene (now Prometics), was listed in The Krever Inquiry as a "rare circumstance". An operation such as CPR, as a commercial plasma collector, is a direct competitor to CBS and is not a "rare circumstance." The distinction of the Winnipeg facility is widely understood by CBS, Hema-Quebec, Health Canada and blood policy experts.
https://www.canada.ca/en/health-canada/corporate/about-health-canada/activities/responsibilities/commissions-inquiries.html
- **"The World Health Organization recommendations only suggest voluntary plasma for transfusion, not for plasma-derived manufactured drugs."** False. Please see WHO expert panel document.
http://www.who.int/bloodsafety/Expert_Consensus_Statement_Self-Sufficiency.pdf
- **"Krever is out-dated we should rely on *The Dublin Consensus* to guide public policy."** Health Canada has used *"The Dublin Consensus"* as "evidence" to support their decision for private plasma collectors in Canada. It is a three-page Big-Pharma backed position paper that has been fostered and subsequently written by members of the **Plasma Protein and Therapeutics Association**. It is not a scientific document. It was not generated by CBS or Health Canada. It has absolutely no Canadian data associated to it. It is exceptional that CBS and Health Canada promoted this "document" on such a high-level policy issue. Please see videos on our FAQ section of our BloodWatch.org website with Dr. Sher, CEO of CBS, detailing the importance/relevance of Krever today.
http://www.pptaglobal.org/about-us/current-members

BloodWatch...

CC: Right Honourable Justin Trudeau / Gerald Butts / Katie Telford

CC: Minister Petitpas-Taylor / Simon Kennedy

CC: Hon. Jagmeet Singh / Hon. Andrew Scheer / Hon. Don Davies / Hon. Marilyn Gladu

CC: Minister Hoskins / Minister Hoffman

CC: CBS - Dr. Graham Sher / / CBS Board of Directors /

References:

https://www.theglobeandmail.com/news/national/ottawa-approved-for-profit-plasma-clinic-despite-warning/article35860933/

http://www.europeanbloodalliance.eu/

http://www.macleans.ca/society/what-a-blood-plasma-for-profit-clinic-means-for-public-heath-care/

http://www.cbc.ca/news/health/plasma-canadian-blood-services-1.3906721

http://www.who.int/bloodsafety/Expert_Consensus_Statement_Self-Sufficiency.pdf

https://www.canada.ca/en/health-canada/corporate/about-health-canada/activities-responsibilities/commissions-inquiries.html

http://www.cbc.ca/news/health/plasma-canadian-blood-services-1.3906721

Canadian Federation of Nurses Unions' Submission to the Expert Panel on Immune Globulin Product Supply and Related Impacts in Canada

Contact: Sebastian Ronderos-Morgan
CFNU Government Relations Officer
sebastian@nursesunions.ca 613-513-7754

Introduction

The Canadian Federation of Nurses Unions (CFNU) represents nearly 200,000 nurses and nursing students across Canada. We are led by our guiding principles: to be the active voice of Canada's unionized nurses, to be strong advocates of public health care, and to improve safety for nurses and the patients for whom we care.

The CFNU is committed to evidence-based research in all the work we do. As frontline health care providers, we believe that the public interest is best served by publicly funded and accountable health care institutions.

Our commitment to a public health care system extends to the life-saving blood products system. Consequently, the CFNU is very concerned by the emergence of for-profit pay-for-plasma clinics in provinces across Canada, established by the company Canadian Plasma Resources (CPR). Canada's nurses firmly support the recommendations of the Krever Report regarding the tainted blood tragedy, as well as the recommendations of the World Health Organization: donors should be voluntary and non-remunerated, and blood should be considered a public resource.

Nurses have first-hand experience with the tragedy that resulted from the poor regulation and the commoditization of blood products. Our members were on the frontlines of the tainted blood crisis, witnessing thousands of avoidable deaths and tens of thousands of unnecessary infections during the 1980s and 1990s. Nurses in Canada continue to treat patients suffering from Hepatitis and HIV contracted from tainted blood.

The Expert Panel has been given the responsibility of studying the adequacy of the supply of immune globulin proteins, as it relates to the emergence of for-profit and pay-for-plasma clinics. The CFNU believes it is vital that the growing demand for immune globulin proteins and other plasma-derived products be met. However, this growing demand can and should be met exclusively by an expansion in the collection capacity of the public agency Canadian Blood Services (CBS) and not by an organization whose goal is to maximize profits.

Response to Submission Questions

Since the issue re-emerged in 2013, the CFNU has consistently stood up for the public blood system and against for-profit pay-for-plasma clinics. Our organization has written letters to the editor, letters to

provincial and federal ministers, and we have participated in high-profile press conferences on Parliament Hill to voice our opposition to the privatization of Canadian blood.

The CFNU's position on this matter is grounded in the important legacy of the Krever Inquiry. We believe Krever's recommendations must be a guiding light for Canada's system of collection and supply of blood products.

In his report, Justice Krever recommended the establishment of CBS as a national and arm's-length public organization responsible and accountable for the blood supply. CBS was to be governed by five basic principles[i]:

1. *Blood is a public resource.*
2. *Donors of blood and plasma should not be paid for their donations, except in rare circumstances.*
3. *Whole blood, plasma and platelets must be collected in sufficient quantities to meet domestic needs for blood components and blood products.*
4. *Canadians should have free and universal access to blood components and blood products.*
5. *Safety of the blood supply system is paramount.*

In the wake of a blood tragedy that destabilized the public's trust, these principles were designed to re-build public confidence in the lives-saving blood system. To maintain this confidence and avoid a repetition of the tragedies of the past, these principles must guide policymaking for Canada's blood products system.

Canada's nurses are deeply concerned by the emergence of for-profit plasma collection clinics offering payment to virtually any Canadian. The introduction of the profit motive (both for the private company and the paid donors) puts at risk not only the safety of the blood products collected but also the security of the supply to Canada's public blood agency, CBS.

While technology exists to disinfect plasma products to ensure that certain pathogens are not present, the introduction of the profit motive necessarily renders safety a secondary priority. Technologies can never provide a 100 percent guarantee of protection from unknown sources of infection. It is for this reason that, despite existing technology, global standards for blood products collection call for systems to be exclusively supplied by voluntary and altruistic donors.[ii] The removal of money from the blood donation transaction reduces the likelihood of dishonesty in the screening process.

Equally, pay-for-plasma clinics also threaten the security of the supply to Canada's existing, robust and trusted CBS system. A 2013 report by the European Blood Alliance found that donors in Germany and Austria left the public voluntary system in favour of the for-profit pay-for-plasma systems in those countries.[iii] In effect, a donor gained by the private paid system was often a donor lost to the public voluntary system. Likewise, in late 2016, reports emerged of a decline in donors at CBS's collection facilities in Saskatoon, following the opening of the nearby paid plasma CPR centre.[iv] This was followed by a letter from the Chair of the Board of CBS to former Health Minister Jane Philpott, in January 2017, expressing concerns that an expansion of CPR's clinics could undermine CBS's donor base.[v]

Between domestic and international evidence, it is clear that, at the very least, CPR clinics threaten the supply of donors to Canada's public system built in the wake of tainted blood. For Canada's nurses, this is unacceptable.

Since 2014, Ontario and Alberta have passed laws banning payment for all blood product donations. The British Columbia Minister of Health has also publicly committed to doing the same.[xi] The message is clear: these provinces are motivated by a commitment to the public interest in blood policy. They also seek to uphold their commitment to the Guiding Principles of the CBS Memorandum of Understanding, to which all provinces and territories, except Quebec, are signatories.[xii]

Worldwide demand for therapeutic immune globulin proteins has been on the rise for years.[xiii] Notwithstanding knowledge of this, CBS regrettably closed plasma collection[xiv] capacity at a time when demand for plasma proteins was rising. This likely caused the gap to grow wider, proving that CBS can ramp up collection to meet the growing demand. Encouragingly, CBS now has a plan to do just that.[xv]

CBS recently announced $100 million per year plan, over seven years, to boost plasma collection from unpaid donors by opening an additional 40 collection centres across Canada.[xvi] Through this announcement, the CBS leadership is clearly and unequivocally targeting a solution to the problems of supply of immune globulin proteins. The CFNU encourages the Expert Panel to promote this initiative as a solution to concerns about the supply of immune globulin proteins. Similar to the success stories seen in countries such as the Netherlands[xvii] and New Zealand,[xviii] CBS's plasma plan has the potential to reduce Canadian reliance on foreign sources of plasma proteins. Moreover, with CPR selling Canadian-sourced plasma internationally,[xix] surely the key to securing Canada's immune globulin supply lies with CBS – an organization with a mandate to supply blood products first and foremost to patients in Canada.

For nurses, public health and safety are our twin bottom lines. If a supply shortage exists for blood products, policymakers must turn to CBS first to find the solution.

Sources:

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i https://lop.parl.ca/content/lop/researchpublications/prb0814-e.htm
ii http://www.who.int/bloodsafety/voluntary_donation.pdf
iii https://tsq.com/blog/publications/blog/__blood_and_cells_from_human_origin
iv http://www.cbs.ca/en_ca/Pages/Canada's-blood-services-2.aspx
v http://www.cbs.ca/en_ca/Pages/Canada's-blood-services-2.aspx
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viii http://bloodwealth.org/wp-content/uploads/2013/04/WHO-CBS-Governments.pdf
ix https://www.cbs.ca/Vision%20to%20Action%20-%20Canada's%20Blood%20System%20Strategic%20Plan%20-%20Year%20Seven%20Update%20-%20EN.pdf
x http://www.cbs.ca/en_ca/Pages/Canada's-blood-services-2.aspx
xi https://globalnews.ca/news/1608111/b-c-expands-ontario-blood-ban-to-ban-plasma-payments-canadian-plasma-protein-products/
xii https://www.theglobeandmail.com/news/national/b-c-minister-says-province-to-ban-paying-for-blood-plasma/article19930139/?ref=http://www.theglobeandmail.com&
xiii https://www.bancorp.net/media/1809.pdf?m=635470209730000000
xiv https://www.nzblood.co.nz/news/2014/new-zealand-blood-service-a-gold-standard-service/
xv http://www.cbc.ca/news/canada/new-brunswick/new-brunswick-health-coalition-blood-donation-plasma-1.4003109

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Date: October 3, 2017

To: Expert Panel on Immune Globulin Product Supply and Related Impacts in Canada

Contact: Adrienne Silnicki, National Director, Policy and Advocacy
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Thank you for this opportunity to provide input to the panel, we are interested in continuing our participation in the Panel's consultation process. The Canadian Health Coalition (CHC) is concerned about the continued payment for blood plasma in Canada.

The CHC is a public advocacy organization dedicated to the preservation and improvement of public health care. Our membership is comprised of national organizations representing health care workers, seniors, churches, anti-poverty groups, students and trade unions, as well as affiliated coalitions in 9 provinces and one territory.

Blood plasma is the first body part in Canada that has been allowed for sale. Canada is only the fourth country in the world to pay plasma donors. The payment of donors goes against the advice of major international health care organizations like the World Health Organization, the International Red Cross and Red Crescent Society, the European Blood Alliance and many others. It also goes against the advice of Canada's Krever Inquiry which looked into ways to ensure that Canada never experienced a catastrophe like the 1980's tainted blood scandal.

The CHC has very serious concerns about the potential impact of a private, paid plasma collector in Canada. We have had communication with Canadian Blood Services (CBS) supporting their plan to increase voluntary donor plasma collection. The CHC has also presented several times to the CBS board and at its stakeholder meetings flagging our concerns.

The Canadian government has claimed that: "Canada and Héma-Québec have been unable to collect sufficient plasma to meet today's plasma product needs through the voluntary model (the Honourable Jane Philpott, Letter to Canadian Health Coalition Chairperson Pauline Worsfold, March 16th, 2016) This reasoning has four serious flaws:

1. CBS only collects plasma at 7 facilities across Canada. In 2012, CBS closed a plasma collection centre in Thunder Bay citing: due to "new replacement products and the decline in hospital demand...based on current projections CBS must plan for a reduction of approximately 10,000 units to our plasma collection program." (Canadian Blood Services, Statement, 2012) The unwillingness to scale up the collection of plasma is not the same as the inability to collect more plasma. CBS is capable of collecting more plasma from voluntary donors, in fact they have created a plan to expand their plasma collection to 40 new sites in the next few years. Health Canada and the provinces and territories should support CBS in this venture, not force them to compete against a private, for-profit model.

   Canadian Blood Services has never run a robust plasma collection system in Canada. Most

Canadians are not aware of plasma or its life saving abilities. Canadians needs to be made aware of the need for plasma, where they can donate and its process. Some countries have developed donor engagement models which include text messages when their blood or plasma has been used to save a life or treat a patient. There are many unique donor recruitment and retention initiatives that need to be explored.

2. Having a parallel private collection system has shown to decrease plasma being donated at volunteer clinics. Previous to 2016, we only had international examples of this from Austria and Germany (European Blood Alliance. Competition in the EU Blood Component Market. January 19, 2009. pp 1-2. https://ebaweb.files.wordpress.com/2012/08/eba-position-paper-competition-in-european-blood-component-market-final.pdf) Now, CBS is reporting a decrease in the most desirable age cohort for blood donors (17-24 years) at their Saskatoon clinic which they believe may be a direct result of the opening of a paid plasma centre. (Canadian Blood Services, Summary Note- Saskatoon Performance and CPR Impacts, April 20, 2017)

3. Canadian Plasma Resources (CPR), the for-profit private company collecting plasma has said that they are looking for purchasers in Europe. The plasma that CPR is collecting will leave Canada and be sold on the international market (http://www.cbc.ca/news/canada/new-brunswick/pay-for-plasma-clinic-recruit-donors-1.4080540). This will not increase the supply of plasma for Canadian use. Private, paid-plasma centres will take donors away from CBS and will sell the plasma on the international market, thereby decreasing the supply available to Canadians.

4. Lastly, once plasma from Canada is sold internationally, trade agreement rules will make it difficult for Canada to stockpile plasma solely for national use and will need to continue selling plasma to the highest bidder. In the event of another blood-borne virus, Canada will not be able to ensure we have enough supply for our own population.

The CHC continues to have very serious concerns about a private, paid plasma collector in Canada. Health Canada has the statutory duty to assess the safety of drugs, including blood, whole plasma and plasma products. Only Health Canada, and not any province or territory, has the legal authority to protect all Canadians from the inherent health hazards of plasma sourced from a population shown by research evidence to have higher rates of infection, that is, paid donors.

Despite current technology, the World Health Organization, European Blood Alliance, International Red Cross and Red Crescent Society continue to call for plasma to be 100 per cent collected from only voluntary donors. While we can protect recipients from known blood-borne illnesses, we cannot detect and treat what is unknown.[1] Canada must draw from only the lowest risk donor pool. Paid plasma donors are a less safe option.

Private, for-profit plasma also poses a risk to vulnerable populations and communities. Canadian Plasma Resources (CPR) has set up an aggressive strategy to draw donors in need of financial assistance. CPR has established their clinics next to homeless shelters and methadone treatment centres, on streets rampant with payday loan centres and pawn shops. In Saskatoon, they advertise for donors above the urinals on university campuses.

The Canadian Health Coalition has been speaking with Canadian Blood Services workers across the country and we have been told that many donors are confused by the similar name, logo (both are blood drops), and slogan used by Canadian Blood Services ("it's in you to give") and Canadian Plasma Resources ("give plasma, give life"). Many donors think they are giving to a public plasma collector for use in country, when in fact they are selling their plasma to a company to profit off it on the global market.

[1] In 2016, Puerto Rico had to shutter its plasma collection centres and import all of its plasma until a screening test for Zika could be developed. http://www.bloodsource.org/News/News-Releases/News-Release-Puerto-Rico

On August 4, 2017, the CHC chair wrote to then Health Minister Jane Philpott and to Abby Hoffman, Assistant Deputy Minister, Strategic Policy Branch at Health Canada, mentioning she was pleased to hear about the establishment of the Panel and requesting that Health Canada considers Dr. Michèle Brill-Edwards M.D. and Dr. Gail Rock M.D. as people to join the panel. It is our belief that both Dr. Brill-Edwards and Dr. Rock would bring to the panel a wealth of experience with Canada's pharmaceutical and blood and plasma system. We hope the panel does reach out to include them in seeking future opinions.

Thank you for the opportunity to submit our concerns to the Expert Panel. We are interested in continuing our participation in the Panel's consultation process.

Canadian Labour Congress Submission to the Expert Panel on Immune Globulin Product Supply and Related Impacts in Canada

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Introduction

The Canadian Labour Congress (CLC) is the largest labour organization in Canada, representing over 3.3 million workers, and bringing together Canada's national and international unions, provincial and territorial federations of labour and over 130 district labour councils.

The labour movement advocates for issues that affect the health and well-being of our union members, and for all Canadians. The CLC has a policy to stop all privatization of our public health care system. For-profit pay-for-plasma clinics is the privatization of an area of our healthcare system and undermines the efforts of Canadian Blood Services (CBS) which is mandated to manage the national safety and supply of blood and blood products.

The Canadian Labour Congress is very concerned with the developments in the expansion of for-profit pay-for-plasma clinics – the latest which opened its doors in July 2017 by the company Canadian Plasma Resources (CPR).

The first for-profit pay-for-plasma clinic by CPR was established in Saskatoon in February 2016. The CPR clinics are paying between $25 and $75 each plasma collection, with increasing payments for increasing number of collections per person. The company locates their clinics in areas where vulnerable and low-income Canadians live. This company intends to proliferate 8 additional for-profit pay-for-plasma clinics in the future.

We are concerned about the safety, security and sustainability of plasma for Canadians, and in Canada. In Canada we do not sell body parts such as organs or tissue, we should not be selling blood or blood products such as plasma.

1. Supply and demand factors that may affect the security and sustainability of the Ig supply for Canadians

In the 1980s, Canadians dealt with a scandal where our blood supply had become tainted, infecting 30,000 Canadians with HIV and Hepatitis C. This led to the Krever Commission that made numerous recommendations to safeguard Canadians. The Krever Commission very clearly stated that blood collected must be from voluntary unpaid donors.

Currently, Canada collects enough plasma through voluntary unpaid donors for fresh plasma transfusion through CBS. However, not enough plasma is collected to create medicines derived from plasma. In the past, CBS has shuttered some of their voluntary unpaid plasma clinics. However, CBS recently announced the goal of collecting half of all the needed plasma for Canada by 2024 through voluntary unpaid donors. CBS is aiming to open 40 new unpaid plasma clinics and draw upon 144,000 new voluntary donor.

However, immediate actions are needed to stem the predatory advances of the for-profit pay-for-plasma company CPR if CBS is to succeed.

2. The potential impact of plasma collection activities on the security and sustainability of the Canadian blood supply, if plasma collections were to expand significantly in Canada

For-profit pay-for-plasma threatens the supply and sustainability of blood and blood products in Canada as:

- More people go to the for-profit clinics, and fewer voluntary unpaid donors go to donate blood and plasma. According to CBS, the number of voluntary unpaid donors dropped in Saskatoon since the opening of the for-profit pay-for-plasma clinic.
- It undermines efforts to make the Canadian blood and blood products supply sustainable as fewer voluntary unpaid donors will mean that less will be collected
- Without a sustainable blood and blood product supply, Canada is vulnerable to the countries that sell to Canada products derived from plasma.

The supply and sustainability of Canada's blood and blood products must be adequate enough to ensure access and safety for all Canadians. This is clearly at risk with the proliferation of for-profit pay-for-plasma clinics.

Currently, only Alberta, Ontario and Quebec have banned payment for blood and blood products.

3. Current and emerging international practices and lessons learned about mitigating any potential detrimental impacts on security and sustainability identified in 1 or 2 above

As a result of the Krever Commission, CBS was set up to manage the national blood and blood products supply and safety, collected entirely from voluntary unpaid donors. In fact, the World Health Organization, the International Red Cross and Red Crescent Societies, and the European Blood Alliance all aim for completely voluntary, non-remunerated blood collection. The reason for international bodies to have this goal is based on evidence which show that a paid system competes with and erodes the voluntary blood collection system.

The for-profit pay-for-plasma company, CPR, sells the plasma collected to the United States and other countries for processing into products. Canada buys 75% of the products that come from paid plasma collected in the United States. Unfortunately, there is a growing demand and dependence across the world for United States plasma products. This situation leaves Canada and Canadians vulnerable in the event of a disruption in supply from the United States.

Recommendations

1. Canada must adhere to the recommendations of the Krever Commission that include collecting all plasma from non-remunerated voluntary sources.

2. Call on the federal Health Minister to have Health Canada place a moratorium on granting new or pending licenses to Canadian Plasma Resources, or any other for-profit companies for for-profit pay-for-plasma clinics.

3. Call on provincial governments to enact legislation banning payment for blood and blood products as they have in Alberta, Ontario and Quebec.

4. Support Canadian Blood Services in their renewed efforts to open 40 new unpaid plasma clinics and draw upon 144,000 new voluntary donors to ensure that Canada collects half of all the plasma needed by 2024.

CUPE Canadian Union of Public Employees

Submission

to the

Expert Panel on Immune Globulin Product Supply and Related Impacts in Canada

of

Health Canada

by the

Canadian Union of Public Employees

October 2017

About CUPE

The Canadian Union of Public Employees (CUPE) is Canada's largest labour union, representing over 650,000 members across the country. CUPE workers take great pride in delivering quality public services in communities across Canada through their work in health care, emergency services, education, early learning and child care, municipalities, social services, libraries, utilities, transportation, airlines and more.

Contact Person for Submission

Amanda Vyce, Senior Research Officer, CUPE National, avyce@cupe.ca

CUPE Members and Canadian Blood Services

CUPE and the Hospital Employees Union, our health care division in British Columbia, represent 500 Canadian Blood Services (CBS) workers in New Brunswick, Alberta, and British Columbia. Our members are at the forefront of Canada's national blood system. They are the point of contact that connects volunteer blood donors to CBS. Furthermore, they help protect the health of Canadians because they ensure the country's blood supply is safe.

In 1997, the Krever Commission established five principles upon which Canada's national blood supply system must be based:

1) Blood is a public resource.
2) Donors should not be paid.
3) Sufficient blood should be collected so that importation from other countries is unnecessary.
4) Access to blood and blood products should be free and universal.
5) Safety of the blood supply system is paramount.

CBS currently collects 100% of the plasma needed for transfusions from unpaid donors, but only 17% of the plasma needed for lifesaving immune globulin (ig), which is in high demand. The other 83% of Canada's plasma supply comes from plasma provided by paid donors in the United States.[1]

In 2010, the World Health Organization (WHO) and the International Federation of Red Cross and Red Crescent Societies (IFRC) developed a global framework agreement for all countries to have 100% voluntary blood and plasma donations by 2020.[2] When it comes to the voluntary collection of plasma, Canada has a lot of work to do to achieve this goal.

CBS plans to increase Canada's plasma sufficiency to 50% by 2024. Its plan includes opening 40 new plasma collection sites and attracting at least 144,000 new plasma donors annually.[3] CUPE and the CBS

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[1] Canadian Blood Services, "Canadian Blood Services proposes ambitious plan to ensure a secure supply of Canadian plasma for immune globulin," https://blood.ca/en/media/canadian-blood-services-proposes-ambitious-plan-ensure-secure-supply-canadian-plasma-immune-globulin (January 24, 2017).
[2] World Health Organization, *Towards 100% Voluntary Blood Donation: A Global Framework for Action*, https://www.ncbi.nlm.nih.gov/books/NBK305667/pdf/Bookshelf_NBK305667.pdf, 2010.
[3] Canadian Blood Services, "Canadian Blood Services proposes ambitious plan to ensure a secure supply of Canadian plasma for immune globulin," https://blood.ca/en/media/canadian-blood-services-proposes-ambitious-plan-ensure-secure-supply-canadian-plasma-immune-globulin (January 24, 2017).

workers that CUPE represents, support the expansion of CBS's plasma collection services to improve Canada's self-sufficiency. But, we strongly oppose the move to commercialize and privatize Canada's collection and supply of blood and blood products.

Health Canada authorized Canadian Plasma Resources (CPR) to operate private, for-profit plasma clinics in Saskatchewan and New Brunswick and it is expected that two more sites are set to open in British Columbia. By allowing CPR to operate, Health Canada has disregarded the recommendations of the Krever Commission, the WHO and IFRC global framework agreement on voluntary donations, and the founding principles of CBS that our members strive to uphold.

There is no evidence that the collection of plasma from paid donors will generate self-sufficiency for Canada. The plasma that CPR collects will not be purchased by CBS, but will be sold to global markets. Allowing CPR to operate in Canada does not help our country to secure its own supply of blood and blood products.

Alberta, Ontario, and Quebec have banned the collection of paid plasma. These provinces recognize that the safest blood comes from voluntary, unpaid donors. For CUPE and its members, all other provinces and territories must also introduce legislation that bans paying donors for blood or blood products. This is essential given that the WHO has shown that the lowest prevalence of transfusion-transmissible infections is found among voluntary, compared to paid blood and plasma donors.*

CUPE Research on Paid Plasma

Below are links to research and reports published by CUPE that are relevant to the mandate of the Panel. They address issues related to the:

- Security and sustainability of the supply of blood and blood products to Canadians,
- Risks and impacts of paid plasma collection,
- International practices and lessons learned from outside Canada.

https://cupe.ca/plasma-profit-why-health-canada-allowing-paid-plasma-collection
https://cupe.ca/sites/cupe/files/plasma-for-profit-march-2016.pdf
https://cupe.ca/cupe-and-allies-say-no-profit-plasma
https://cupe.ca/cupe-nb-executive-unanimous-there-should-be-no-paid-plasma-nb
https://cupe.ca/no-room-profit-our-blood-system-stop-creating-precarious-work
https://cupe.ca/take-action-world-blood-donor-day-june-14

CUPE's Position on Paid Plasma

As noted above, CUPE and the CBS workers that it represents oppose paying donors for blood and blood products. We support the CBS' plan to expand its voluntary plasma collection services across Canada to help the country move closer towards self-sufficiency in blood products and to ensure the safety of our blood supply.

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* World Health Organization, *Towards 100% Voluntary Blood Donation: A Global Framework for Action*, https://www.ncbi.nlm.nih.gov/books/NBK305667/pdf/Bookshelf_NBK305667.pdf, 2010

To support the expansion efforts of CBS, CUPE calls on the Minister of Health, Ginette Petitpas Taylor, to use her statutory duty under the federal *Food and Drugs Act* to designate payment for plasma as a safety issue. We further call on Health Canada to cancel all licenses granted or pending to Canadian Plasma Resources (CPR) across the country.

Allowing CPR or any other private, for-profit blood collection enterprise to pay people for their plasma will weaken the voluntary donor base participating in our public blood supply system. This has already occurred in Saskatchewan where the number of donations in the province has declined since CPR opened its doors there in February 2016.

Private paid plasma clinics directly hamper the efforts of CBS to grow its base of voluntary plasma donors and to move Canada closer towards the goal of self-sufficiency. Health Canada should not make CBS compete for donors against the private interests of for-profit companies.

CBS staff care about the organization they work for and CBS donors. They are ready to help CBS to grow its base of voluntary plasma donors. However, in recent years, CBS has not only cut hours for collection, it has also closed clinics as part of its Lean management model. As noted, CBS has indicated that it plans to open new sites across Canada, which CUPE supports. However, the opening of 40 sites may not be enough to expand collection services beyond the levels that existed prior to the clinic closures.

The majority of CBS clinic employees are precariously employed, working part-time, irregular hours. Our members have urged the board of CBS to expand the hours of existing CBS clinics, as well as staffing levels, to meet their collection goals. Increasing the number of full-time positions and the number of hours for part-time workers would not only make plasma collection clinics more accessible to existing and potential donors, it would also improve other conditions at the clinics, such as long wait times that result from overbooking. Both factors will enhance the efforts of CBS to attract new and to retain current donors, which are imperative to achieving self-sufficiency.

Having a stable workforce will assist CBS' efforts to restructure and grow. The workflow, schedules, experience, training, and the number of clinic staff all have a direct impact on donor experience. Everyday, CUPE members see that staff shortages, irregular schedules, and precarious working conditions at CBS clinics have a negative impact on donors. They result in increased donor wait times, the loss of donated blood when standard operating procedures are not followed, and an inability to retain donors on a regular basis.

By improving the security and stability of its workforce, CBS will be able to enhance the quality of its services. Staff will feel valued by the organization. They will be able to take a stronger role in motivating donors to give on a regular basis because they will have more time to acknowledge donors and to let them know that their commitment to our blood system is valued and appreciated. Improving the working conditions at its clinics will help CBS to reach its goals of moving Canada closer towards self-sufficiency in blood and blood products.

Restructuring and expanding are real challenges for any organization. But small changes can have a big impact. CBS workers who are CUPE members are vested in the success of our national blood system. By positively investing in and showing a real commitment to its workforce, CBS can achieve significant changes that will expand Canada's voluntary base of blood donors and enhance its capacity to save lives through its blood supply system.

[illegible]

THE COUNCIL OF CANADIANS | LE CONSEIL DES CANADIENS

ACTING FOR SOCIAL JUSTICE | AGIR POUR LA JUSTICE SOCIALE

The Council of Canadians' submission to the Expert Panel on Immune Globulin Product Supply and Related Impacts in Canada

Contact: Angela Giles
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October 06, 2017

Dear esteemed members of the Expert Panel,

Who we are and our interest in paid plasma

The Council of Canadians is Canada's leading social action organization with over 100,000 grassroots supporters and 60 local chapters from coast to coast. Through our campaigns, we advocate for clean water, green energy, fair trade, public health care and a vibrant democracy. We educate and empower people to hold our governments and corporations accountable.

We are supported by individual donations from ordinary Canadians and do not accept funding from corporations or government.

For over four years, we have been speaking against for-profit blood and plasma collection in Canada. Our chapters have been raising the issue in their communities, as private clinics get proposed or open in their province. We have promoted the creation of legislation in provinces where private companies have applied for appropriate licensing to open paid plasma clinics, and have celebrated when Ontario and Alberta (and Quebec) did create the legislation banning private clinics.

Fundamentally, the Council of Canadians believes everyone should have access to the same health care services and quality of care provided by a national, public system. A public system by definition is the opposite of for-profit, and we have seen this industry benefitting on the backs the most vulnerable in society. We believe the unbalanced power of corporations must be challenged and we do not believe corporations have a place in health care in this country (and certainly not the market of organs, tissue, blood or blood products). We are very concerned that licenses have been issued by Health Canada allowing private clinics run by Canadian Blood Resources to open in Saskatchewan and New Brunswick, which seems to us a blatant disregard for the outcomes of the Krever Commission[1].

Socio-economic impacts

The tainted blood scandal of the 1980s will forever be a scar in the history of this country. The Krever Inquiry that followed brought forth many recommendations to safeguard our society, including that

only one national operator collect blood and plasma on behalf of Canadians and that no part of the national blood services duties be contracted out to others, and that donors should not be paid.

Canadian Blood Services (CBS) took over management of the Canadian blood system in 1998 and was founded on the principles laid out by Krever's recommendations, including accountability, engagement and transparency.

The World Health Organization (WHO) in 2010 released the recommendation that all countries support blood and blood product collection be 100% voluntary (unpaid) donations by 2020.

Canadian Plasma Resources has shown their exploitative nature by opening clinics next to a homeless shelter and a methadone clinic in Ontario (before the legislation banning paid plasma clinics).

Allowing a for-profit industry to enter the Canadian system threatens this volunteer base and flies in the face of Krever and the WHO. Canadian Plasma Resources does not have an agreement with CBS to sell its' products to the Canadian market and will therefore need to go to external markets, shortchanging the Canadian system even further by effectively removing unpaid volunteers.

Summary

Policies and decisions made regarding blood and blood products in Canada should be based on prioritizing the safety of donors and recipients, and protecting the Canadian blood system overall. The Council of Canadians, our supporters and chapters oppose privatization in health care overall and plasma specifically, and will continue to work with people in communities to achieve legislation to ensure the public system is protected at a provincial and federal level.

We appreciate this opportunity to contribute to the discussion on this important public policy decision, and trust that you as the Expert Panel will work to ensure the protection of the health and safety of the public. We truly hope the work of this panel will result in recommendations to the Federal government to maintain the unpaid volunteer base and to establish clear blood policies.

Sincerely,

Angela Giles
Atlantic Regional Organizer
The Council of Canadians

[1] Documents relating to the Krever Commission, Government of Canada website. https://www.canada.ca/en/health-canada/corporate/about-health-canada/activities-responsibilities/commissions-inquiries.html

New Brunswick Health Coalition submission to

The Expert Panel on Immune Globulin Product Supply and Related Impacts in Canada

The New Brunswick Health Coalition (NBHC) is a public advocacy organization dedicated to the preservation and improvement of public health care. Membership in the NBHC is open to all groups and individuals in New Brunswick who share the objectives of NBHC. The following represents the NBHC's position regarding blood and plasma collection.

A single national system

Following the contaminated blood scandal, Justice Krever proposed a single national system for the collection of blood and blood products. Those recommendations gave birth to Canadian Blood Services which replaced the Canadian Red Cross. Recommendations 3 and 4 of the Krever Report:

3. *It is recommended that Canada have a national system for the collection and delivery of blood components and blood products.*
4. *It is recommended that the core functions of the national blood supply system be performed by a single operator and not be contracted out to other.*[i]

Public resources and paid donors

Justice Krever's Report, the World Health Organization and Canadian Blood Services all state that blood and plasma are a public resource and should not be collected from paid donors. Allowing private, for-profit companies, who consider plasma as a private resource and who will pay donors, goes against the report and these organizations.

Recommendation 2 of Justice Krever's Report on contaminated blood:

It is recommended that the Canadian blood supply system be governed by five basic principles:

a) *Blood is a public resource.*
b) *Donors of blood and plasma should not be paid for their donations, except in rare circumstances.*
c) *Whole blood, plasma, and platelets must be collected in sufficient quantities in Canada to meet domestic needs for blood components and blood products.*
d) *Canadians should have free and universal access to blood components and blood products*
e) *Safety of the blood supply is paramount.*[ii]

The World Health Organization has the same position. In 2012, the World Health Organization produced a report: *Expert Consensus Statement on achieving self-sufficiency in safe blood and blood products based on voluntary non-remunerated blood donation (VNRBD).*[iii] The report states: "*Blood, plasma and cellular components and other therapeutic substances derived from the human body should not be considered as mere ''commodities''. Donated blood that is provided voluntarily by healthy and socially committed people is a precious national resource.*"

The report gives a clear definition of what is a voluntary non-remunerated blood donation, "*Voluntary non-remunerated blood donations (VNRBD) means that a person gives blood, plasma or cellular components of his-her own free will and receives no payment for it, either in the form of cash, or in kind which would be considered s substitute for money. This could include time off work other than that reasonably needed for the donation and travel. Small token, refreshments and reimbursement of direct travel costs are compatible with voluntary non-remunerated donation.*"[iii]

Canadian Blood Services agrees. In its May 5, 2016 news release, it stated, "*Canadian Blood Services does not and will not pay donors for blood, plasma or any other kind of donation.*"[iv]

Accountability to Canadians

Justice Krever's Report, recommendation 10, stresses the importance of a publicly administered system, and Canadian Blood Services states its public obligation of being accountable, *"it is recommended that the blood supply system be publicly administered by a national blood service, a corporation to be created by an Act of parliament."*[v]

In its January 24, 2017 news release the Canadian Blood Service specified, *"Plasma, just like whole blood, is a public resource that must be safeguarded for Canadians. Long-term security of the plasma supply for Ig (immune globulin) can only be achieved through increased plasma collection by the publicly funded and publicly accountable not-for-profit blood system operated by Canadian Blood Services."*[vi]

Private, for-profit companies are not accountable to the public or to decision makers and should not be allowed to operate in Canada.

Impact on the system based on voluntary non-remunerated blood donors (VNRBD)

Having, as a competitor, a plasma collection system based on paid donors will have a negative impact on blood and plasma collection based on voluntary donors. The World Health Organization is worried: *"There are concerns that sufficient safe donations and sustainable supply, availability and access to blood and blood products based on VNRBD may be compromised through the presence of parallel systems of paid donations."*[vii]

Canadian Blood Services CEO, Graham Sher said in an interview on CBC, December 21, 2016, *"There's marked confusion as to who is operating in the Saskatoon market" said Dr. Graham Sher, CEO of CBS. Donor numbers have also dropped in that city."*

"We've begun to see some early impacts of having this private, for-profit enterprise operate in our jurisdiction," Sher said. "It is early evidence, but it's certainly consistent with what other countries are seeing when you see large-scale ramp-up of the paid plasma industry side by side with the blood industry.

"We in Canada are at risk, if we don't collect more of our own plasma, then we're not going to be able to access the global supply of these plasma drugs," he said.

"We have to collect more plasma, control it, and keep it in Canada for Canadian patients, which the private industry is not obligated to do. They will sell to the highest bidder."

Michael Decter was an adviser to the Krever Commission into the tainted blood scandal, and is a former deputy health minister in Ontario, "As an economist, I'm not surprised that once you allow paid plasma donation in, it's going to undercut the volunteer sector," Decter said."[viii]

Security of the supplies

Presently, Canadian Blood Services collects enough blood and plasma to meet the needs of Canadians. However, it does not collect enough to be able to produce plasma-derived drugs. The coming of competitors for plasma donors goes against that plan. It is important to note that New Brunswick contributes, like all the other provinces, to funding Canadian Blood Services and has the responsibility of supporting a public system, not a private one. Canadian Blood Services proposed in its January 24, 2017 news release, a plan to increase its Canadian plasma supplies:

Canadian Blood Services has shared an ambitious plan with governments outlining how we will ensure a safe and secure supply of plasma needed to manufacture immune globulin (Ig) for Canadian patients. The plan provides a roadmap for significantly increasing the amount of plasma we collect from Canadian donors, as per our voluntary, non-remunerated (unpaid), publicly funded collections model.

Canada is self-sufficient in plasma for transfusions. However, we only collect enough plasma to meet about 17 per cent of the demand for Ig, a critical lifesaving drug. Our goal is to increase Canada's plasma sufficiency for Ig to 50 per cent. This would mean half of the Ig used by Canadian patients would be made from Canadian plasma.

What will this look like? By 2024, this could mean as many as 40 new plasma collections sites collecting more than 600,000 litres (more than 866,000 units) of plasma per year. Upwards of 144,000 new plasma donors will be needed annually to collect the significant additional volume of plasma the plan calls for.[ix]

Moreover, the plasma collected by Canadian Plasma Resource would not be used to meet our needs because Canadian Blood Services has stated it will not buy plasma from Canadian Plasma Resource.[x] Consequently, the plasma collected by private companies from the veins of Canadians will be sold on international markets and will not help us become self-sufficient.

Vulnerable populations

It has become obvious that two segments of the population are targeted by private companies to be donors: students, because donations are allowed at 17 years of age, and people living in poverty. The World Health Organization says, *"Payment for the donation of blood (including donations of plasma and cellular components) not only threatens blood safety, it also erodes community solidarity and social cohesion that, on the contrary, can be enhanced by the act of voluntary non-remunerated donation. By placing an onus on under-privileged populations in need of money, it also compromises the development of a voluntary, non-remunerated blood donor system."*[xi]

In an interview done by Isabel Teotonio for The Star.com, April 22, 2013, *"Hemophilia Ontario opposed to paid plasma clinics."* The same article notes, *"The company [Canadian Plasma Resources], however, says it hopes to target university students- that is, if it gets the green light to open from both the federal and provincial governments."* If the collection system is endangered by a new infectious threat, not yet identifiable by lab testing, the only way to safeguard against such threat is the voluntary collection of plasma from healthy citizens who have no monetary incentive to lie about their health status.

New Brunswick Organizations supporting NBHC's campaign to oppose private pay-for-plasma clinics:

Association de bibliothécaires, professeures et professeurs de l'Université de Moncton; Association des Universités du 3e âge du NB (AUTAUNB); Association francophone des aînés du NB; Association of University of New Brunswick Teachers; Canadian Federation of Students - NB Representative; Canadian Labour Congress - Atlantic Region; Canadian Union of Public Employees, NB Division; Coalition for Seniors and Nursing Home Residents; Comité de justice sociale des Religieuses NDSC; Conférence Mère Teresa de la Société St-Vincent de Paul; Conseil des sociétés culturelles du NB; Égalité en santé; Fédération des étudiants et étudiantes de l'Université de Moncton; John Howard Society of NB; Justice and Solidarity Committee, Moncton Diocese; Maison de Nazareth.; Mount Allison Faculty Association; NB Common Front for Social Justice; NB Council of Hospital Unions; NB Council of Nursing Home Unions; NB Federation of Labour; NB Federation of Union Retirees; NB Nurses Union; NB Seniors Citizens Federation; New Brunswick Union; Regroupement féministe du NB; Société de l'Acadie du NB; Société des enseignantes et enseignants retraités francophones du NB (SERFNB); United Way of Greater Moncton and Southeastern NB.

Only four countries have a paid donor plasma collection system: USA, Germany, Austria and the Czech Republic. Alberta, Ontario and Quebec have all banned private blood and plasma collection under their voluntary blood donations Acts.

[i] Source: Commission of Inquiry on the Blood system in Canada, Volume 3, Part IV pages 1049 and 1050.
[ii] Source: Commission of Inquiry on the Blood system in Canada, Volume 3, Part IV page 1047.
[iii] Source: http://www.who.int/bloodsafety/transfusion_services/WHO_Expert_Consensus_Statement_Self-Sufficiency.pdf?ua=1
[iv] Source: https://blood.ca/en/media/canadian-blood-services-does-not-and-will-not-pay-donors
[v] Source: Commission of Inquiry on the Blood system in Canada, Volume 3, Part IV, page 1053.
[vi] Source: https://blood.ca/en/media/canadian-blood-services-proposes-ambitious-plan-ensure-secure-supply-canadian-plasma-immune-globulin
[vii] Source: http://www.who.int/bloodsafety/transfusion_services/WHO_Expert_Consensus_Statement_Self-Sufficiency.pdf?ua=1
[viii] Source: http://www.cbc.ca/news/health/plasma-canadian-blood-services-1.3906721
[ix] Source: https://blood.ca/en/media/canadian-blood-services-proposes-ambitious-plan-ensure-secure-supply-canadian-plasma-immune-globulin
[x] Source: Press release, May 5, 2016, Canadian Blood Services
[xi] Source: http://www.who.int/bloodsafety/Expert_Consensus_Statement_Self-Sufficiency.pdf

APPENDIX G

ETHICISTS AND ECONOMISTS

Ethicists and Economists express concerns about banning compensation for plasma donors with regards to ensuring the security of a safe Immune Globulin Product Supply

Submission to the Expert Panel on Immune Globulin Product Supply and Related Impacts in Canada

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Signatories:
Alvin E. Roth, Stanford University, Nobel Prize winner (Economics)
Vernon L. Smith, Chapman University, Nobel Prize winner (Economics)
Aaron Ancell, University of Toronto
Jason Brennan, Georgetown University
Gerald B. Dworkin, University of California, Davis
William English, Georgetown University
David Faraci, Georgetown University
Mark Fedyk, Mount Allison University, The Ottawa Hospital Research Institute
Jessica Flanigan, University of Richmond
Glenn Fox, University of Guelph
Vincent Geloso, Texas Tech University
David R. Henderson, Postgraduate Naval Academy (Emeritus)
Peter M. Jaworski, Georgetown University
J. Paul Kelleher, University of Wisconsin-Madison
Kimberly D Krawiec, Duke University
Nicola Lacetera, University of Toronto
Chris MacDonald, Ryerson University
Mario Macis, Johns Hopkins University
Jonathan Miles, Quincy University
Matthew Mitchell, University of Toronto
Jeffrey Moriarty, Bentley University
Jan Narveson, University of Waterloo (Emeritus), Officer, Order of Canada
Vida Panitch, Carleton University
Jacob Sparks, John Jay College
James Stacey Taylor, The College of New Jersey
Alex Tabarrok, George Mason University
Daniel Waxman, Oxford University

1. INTRODUCTION

1.1 We are professional ethicists in the fields of medical ethics, business ethics, and/or normative ethics, and academic economists who study how incentives and other reward mechanisms affect individual behaviour. We all share the goal of improving social welfare.

1.2 The Provinces of Quebec (1994), Ontario (2014),[1] and Alberta (2017)[2] have passed Voluntary Blood Donation Acts or their equivalents that prohibit, amongst other things, compensation for plasma donations for purposes of further processing into plasma-derived

medicinal products (hereafter: "PDMPs"), like Immune Globulin (hereafter: "Ig"). Currently, the Nova Scotia legislature is debating a Voluntary Blood Donations Act,[3] and the British Columbia government has suggested that it is interested in pursuing similar legislation.[4]

1.3 We have strong reservations regarding any Act or legislation (hereafter: "Acts") that would prohibit compensation for blood plasma donations, where the donated plasma will be processed into plasma-derived medicinal products (hereafter: "PDMPs"), like Immune Globulin (hereafter: "Ig"). (We do not here address blood plasma collected for transfusions or other purposes.) Both the ethical and the economic arguments against a compensatory model for blood plasma for further manufacture into PDMPs (hereafter: "the compensatory model") are weak. Moreover, significant ethical considerations speak in favour of the compensatory model, and therefore against the Acts.

1.4 Below, we respond to the ethical arguments offered in favour of the Acts: that the compensatory model would result in **wrongful exploitation** (§2); that the compensatory model would promote the view that human beings, their bodies, or subparts thereof, are **mere commodities** (§3); and that the compensatory model would incentivize donation for personal gain over donation from **altruistic motives** (§4). We agree with Health Canada, Canadian Blood Services, and all major medical oversight bodies that there are no **safetyissues**

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[1] Text of the Act: http://www.ontla.on.ca/web/bills/bills_detail.do?locale=en&BillID=3015
[2] Text of the Act: http://www.qp.alberta.ca/documents/Acts/O05.pdf
[3] Hansard debate: http://nslegislature.ca/index.php/proceedings/hansard/C98/house_17oct11/#HPage1055 [4] See: https://beta.theglobeandmail.com/news/national/blood-agency-seeking-855-million-in-funding-to-boost-plasma-supply-document-reveals/article35980339/?ref=http://www.theglobeandmail.com&

associated with PDMPs, including Ig, made with paid donors (§5). With regard to the **security** of Canada's supply of PDMPs, including Ig, we note that it has been and currently is overwhelmingly dependent upon the compensatory model, and that this is likely to continue well into the future. Given this fact, we note that the goal of having a **sufficient** quantity of PDMPs, including Ig, is undermined by the Acts (§6). Given the moral urgency of increasing the supply of PDMPs, including Ig, and the weakness of the economic and ethical arguments thus far presented against the compensatory model, we conclude that **the Acts are not justified** (§7).

2. WRONGFUL EXPLOITATION

The Acts are intended, as we understand them, to prevent wrongful exploitation. We agree that wrongful exploitation is a significant worry. Our view is that a practice may be wrongfully exploitative when there is undue risk, undue inducement, or an unfair division of the benefits from an exchange. We do not think that compensation, per se, meets these criteria, and so conclude that a compensatory model need not be wrongfully exploitative.

2.1 Plasmapheresis is a non-invasive procedure. The procedure takes between 60 and 90 minutes per donation. Plasma clinics in both the U.S. and Canada are required to inform donors of any risks. In addition, donors go through medical screening, must provide proof of residence, and have to meet certain weight and age requirements. Additionally, unlike kidneys and other organs for which ethical concerns about wrongful exploitation arise, blood plasma quickly regenerates. Donors do not permanently "lose" a body part. As the burdens here are limited, they do not provide solid grounds for concern about wrongful exploitation based on undue risk.

2.2 Donors receive, on average, $25-50 per donation. In Saskatchewan, where this practice has existed since 1984, donations are compensated at greater-than-minimum-wage levels. Canadian Plasma Resources pays between $25 and $30, while in the U.S., donors receive between $25 and $50 per donation. Compensation is therefore not low, but it is not, on the other hand, so high as to unduly induce a potential donor into a donation. Given that the risks are not undue, and that payment, although not low, is not too high, there is no particularly good reason to worry about wrongful exploitation based on undue inducement.

2.3 Compensation to donors represents approximately 30-40% of the total revenue per 800 mL of blood plasma in Canada and the U.S. Currently, Canadian Plasma Resources receives approximately 0% in profits. Therefore, donors appear to receive the majority of the financial benefits per individual exchange. Faced with these figures, worries about wrongful exploitation based on an unfair division of the benefits of exchange are difficult to substantiate.

2.5 We therefore conclude that worries about wrongful exploitation have weak grounding, whether they are based on undue risk, undue inducement, or a concern about an unfair division of the benefits from exchange.

3. COMMODIFICATION

The Acts are also intended, as we understand it, to avoid promotion of the view that human beings, their bodies, or subparts thereof are appropriately viewed as commodities. Insofar as anything compensated for is a commodity, it is trivially true that the compensatory model promotes the view that blood plasma is a commodity. But this is ethically irrelevant. The relevant ethical concern is that the compensatory model would promote the view that human beings (etc.) are "mere" commodities, meriting no more ethical regard than other mere commodities, such as cars or clothing. However, there is no evidence that the compensatory model would promote this view.

3.1 There is no evidence that compensation for blood plasma donations in, for example, Saskatchewan, the United States, Germany, Austria, Hungary, or the Czech Republic has promoted the view that donors or their blood plasma are regarded as mere commodities. There is as yet no evidence that Saskatchewanians have different attitudes towards their blood plasma than, say, British Columbians currently have.

3.2 Everyone involved in blood plasma donation in Canada – the nurses, the doctors, the administrators, the medical scientists, the professors who study the matter, the chief executives of Canadian Blood Services, the manufacturers of plasmapheresis machines, the fractionators, and so on -- receives compensation, except the donor. There is no evidence that Canadians regard the services so provided, nor the people providing those services, as mere commodities in virtue of the fact that they are financially compensated. For the argument that donor compensation would so promote this view to be compelling, one would need an explanation for why the connection between compensation and commodification applies exclusively to compensating donors, and not to these other forms of compensation. No such explanation has been offered, nor is any apparent or plausible.

3.3 Proponents of the Acts have provided no evidence, empirical or otherwise, that the compensatory model for blood plasma donation, in contrast with similar practices referenced above, would promote the view that donors or their blood plasma are mere commodities, or would be so regarded. We therefore conclude that worries about commodification are not well-grounded.

4. ALTRUISM

The Acts are also intended, as we understand it, to avoid incentivizing donation for monetary gain over donation from altruistic motives. We agree that altruism is desirable, and that we need to be careful when considering policies to preserve and promote altruistic and benevolent motives and actions. However, this argument with respect to this compensatory model is unpersuasive.

4.1 The compensatory model leaves open the possibility of donors' opting out of compensation, or the operation of a parallel non-compensatory model. The United States does

just this, and has an approximately 50% higher voluntary, unpaid, per capita blood donation rate than Canada. Germany, Austria, and the Czech Republic, where plasma donors can be compensated, all have higher rates of voluntary, unpaid per capita blood donation than Canada.[1]

4.2 Compensation and altruism are not mutually exclusive. In many cases, people who are compensated are motivated simultaneously (or even primarily) by altruistic impulses. This is true of many doctors and nurses. There is no reason to believe that a compensated blood plasma donor would be solely or exclusively motivated by personal financial gain.

4.3 Even if the compensation model came with costs in terms of the value of promoting altruistic motivations, this must be weighed against the value of obtaining a sufficient quantity of blood plasma to meet Canada's need for PDMPs, including Ig. Arguably, preventing avoidable pain, suffering, and death among current and future patients is morally more urgent than preserving altruistic motivations amongst donors.

4.4 We therefore conclude that preserving altruistic motivation is not a sufficient reason to object to the compensatory model.

5. SAFETY

Proponents of the Acts refer to the 1980s tainted blood scandal, and to the subsequent Krever Inquiry's findings presented in 1997. Proponents suggest that the safety of the blood supply is suspect when a compensatory model is used. But these claims conflate two separate issues – the compensatory model for blood plasma donations for, on the one hand, further manufacture into PDMPs and, on the other, purposes of transfusion.[2] We remind everyone that the compensatory model for the collection of blood plasma for purposes of transfusion is not at issue. The safety of plasma-derived medicinal products made from paid donors is well-established.

5.1 Health Canada released the following Question and Answer in a Fact Sheet on its website:

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[1] https://www.canada.ca/en/health-canada/services/drugs-health-products/public-involvement-consultations/biologics-radiopharmaceuticals-genetic-therapies/backgrounder-paper-plasma-donations-canada.html (Accessed: Nov. 7, 2017)

[2] "...for transfusion of (cellular) blood components, the collection and assessment of epidemiological data are critical. However, for plasma-derived medicinal products, the relation between a safe medicinal product and donor epidemiology is less straightforward as a result of the virus removing and/or inactivating capacity of the production process." http://www.sciencedirect.com/science/article/pii/S0887796313000357#bib0025 "Viral safety of human plasma-derived medicinal products: Impact of regulation requirements." 2013.

> **Many Canadians taking plasma products were infected with HIV and hepatitis during the years of the tainted blood crisis. The Krever Inquiry Report recommended that blood donors should not be paid. Isn't allowing payment for plasma increasing the risk of another tainted blood crisis?**
>
> No. Lessons of the tainted blood crisis must never be forgotten, and action has been taken since then to help prevent a tragedy like that from happening again. There are no plans to change Canada's voluntary blood for transfusion donor system. However, technological advancements have made plasma products safer. New measures such as heat treatment, filtration or treatment with chemicals have been put into place to remove or inactivate viruses or other contaminants when producing blood products from plasma. There has not been a single case of transmission of hepatitis B, hepatitis C or HIV caused by plasma products in Canada since the introduction of modern manufacturing practices over 25 years ago, despite the fact that most of the plasma donors were paid.[7]

5.2 Dr. Graham Sher, the CEO of Canadian Blood Services, has said, "It is categorically untrue to say, in 2015 or 2016, that plasma-protein products from paid donors are less safe or unsafe. They are not. They are as safe as the products that are manufactured from our unremunerated or unpaid donors."[8]

5.3 We accept the consensus view of medical scientists and professionals represented in the above, that compensating donors does not compromise the safety of PDMPs, including ig.

5.4 With respect to the donors, we accept the consensus view of medical scientists and professionals that donating blood plasma is safe, and agree that Canadians should be encouraged to donate, with or without compensation.[9]

5.5 Canada has been importing PDMPs from the United States where donors are compensated. If there were safety concerns, we would not be engaged in this practice. In addition, proponents of the Acts do not call for a prohibition on the importation of PDMPs made from compensated donors. There is no reason to believe that PDMPs made from compensated Canadian donors would be any less safe than PDMPs made from compensated U.S. donors.

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[7] https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/act-y-tea/fact-sheets/plasma-donation-canada.html (Accessed: Oct. 13, 2017)

[8] "Are products made from paid donors safe?" Canadian Blood Services, YouTube video https://www.youtube.com/watch?v=chet_ZbE?rA&index=3&list=PLOpdDY_C_bdOaGu21eQTKDPFs_j41D_Gb_P (Accessed: Oct. 13, 2017)

[9] See, for example, Crocco, I., Franchini, M., Garozzo, G., Gandini, A.R., Gandini, G., Bonomo, P. and Aprili, G., 2009. Adverse reactions in blood and apheresis donors: experience from two Italian transfusion centres. *Blood transfusion*, *7*(1), p.35. ("In conclusion, the results of our 5-year survey document that apheresis and blood donation are safe procedures for the donor with a low incidence of adverse reactions; the adverse reactions that did occur were mostly mild and resolved rapidly.").

5.6 The risks of harm both to donors of blood plasma and patients who rely on PDMPs, including Ig, are negligible. We therefore conclude that safety concerns are not a good reason to oppose the compensatory model.

5.7 We note that the suggestion that PDMPs manufactured from compensated donations are unsafe is an unfounded allegation that runs contrary to medical expert consensus. Such unfounded allegations may be harmful insofar as they stoke unjustified fears that cause patients to avoid necessary treatments. We therefore caution proponents of the Acts not to imply or suggest that PDMPs made with compensated donors are risky or unsafe. Doing so is arguably unethical.

6. SECURITY

The security of our supply of PDMPs, including Ig, is dependent on paid plasma donors. In 2016, for example, over 80 per cent of our immune globulin was imported from the United States, where donors are paid. Canadian Blood Services expects a doubling of demand for PDMPs by 2020. Even if Canadian Blood Services opens the 40 plasma clinics they have requested funds for, they anticipate meeting, at most, 50 per cent of the domestic demand for PDMPs. They have no plans to stop using PDMPs made with compensated plasma donations.

6.1 It is morally urgent for Canada to have a sufficient quantity of PDMPs, including Ig, to meet the domestic demand for these products. Demand for PDMPs is expected to continue growing, with a 40% increase in global demand by 2020.[9]

6.2 Canada, along with the majority of the rest of the world, currently relies on the U.S., which uses a compensatory model, for the security of its PDMP supply, including Ig.[10]

6.3 The U.S. is able to supply the majority of the world with PDMPs, including Ig, because compensation has enhanced supply. The compensatory model, therefore, currently is essential to Canada's security of PDMPs, including Ig.

6.4 From a moral standpoint, focusing only on Canada may actually be too narrow. Canada should seek to be a net contributor to the global supply of PDMPs, including Ig. The goal of meeting 50% of the domestic need for PDMPs -- the most ambitious hope of Canadian Blood

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[9] See, for example, "Backgrounder: Plasma," Canadian Blood Services. https://blood.ca/en/media/plasma (Accessed: Dec. 15, 2017)

[10] According to Canadian Blood Services, for example: "Today, the amount of plasma we collect only meets only about 17 per cent of the need for intravenous immune globulins (IVIG), the plasma protein products in highest demand by patients. The remaining products we buy come from plasma donated by paid donors in the United States, which is not unique to Canada and ensures security of supply for patients. Without this system, patients who depend on these drugs would not have ready access to the therapies they need." https://www.blood.ca/en/blood/plasma-sufficiency (Accessed: Dec. 15, 2017)

Services should they receive funding for opening 40 additional clinics[12] -- may therefore be perceived as morally insufficient. Canada is in a position to strive to be a net exporter of blood plasma used for the manufacture of PDMPs, including Ig.

6.5 The evidence shows that a compensatory model for plasma is an essential tool for increasing supply.[13] We are skeptical of the claim that a non-compensatory model will promote the security of the supply of PDMPs, including Ig.

6.6 We are similarly skeptical of the claim that the compensatory model would crowd-out voluntary blood donation -- we have not seen sufficient evidence that this is so. Evidence from Saskatoon, where Canadian Blood Services competes directly with Canadian Plasma Resources, is inconclusive.[14]

6.6 We therefore conclude that, because improving the security of Canada's (and the global) supply of PDMPs is morally urgent, a compensatory model should not be precluded. Further, we conclude that jurisdictions that have banned the compensatory model ought to reconsider the Acts as swiftly as possible, and contribute to opening a more comprehensive conversation on the topic before taking impatient measures against the compensatory model.

7. CONCLUSION

7.1 In our view, none of the moral objections to the compensatory model are persuasive. Furthermore, there is a strong moral presumption against standing in the way of a model that is the most likely to promote security not only of Canada's supply of PDMPs, including Ig, but also of the global supply. We urge Quebec, Ontario, and Alberta to reconsider the Acts currently prohibiting compensation in their provinces.

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[12] See Kelly Grant, "Blood agency seeking $855-million in funding to boost plasma supply, document reveals," *Globe and Mail*, August 14, 2017. https://www.theglobeandmail.com/news/national/blood-agency-seeking-855-million-in-funding-to-boost-plasma-supply-document-reveals/article35980339/ (Accessed: Dec. 15, 2017)

[13] For example, see Henry G. Grabowski & Richard L. Manning (2016) An Economic Analysis of Global Policy Proposals to Prohibit Compensation of Blood Plasma Donors, International Journal of the Economics of Business, 23:2, 149-166. ("...compensated plasma donation is important for maintaining adequate and consistent supplies of plasma and limits the risk of under-treatment for the foreseeable future." http://www.tandfonline.com/doi/full/10.1080/13571516.2016.1182690)

[14] Saskatoon has seen a 35.8% increase in new donors, with 1,184 such donors from April-March 2016, and 1,608 new donors in April-March 2017. Canadian Blood Services concludes that "The active donor base and donation frequency for Saskatoon does not show evidence of an impact of CPR's operations on Canadian Blood Services. The active donor base for Saskatoon continues to increase, on an upward trend." Letter to The Honourable Jim Reiter, Minister of Health, Feb. 21, 2017, at p. 7. The letter does note, however, that "The 17-to 24-year-old segment is experiencing a double-digit decline at the Saskatoon site. This could be attributed to CPR and the demographic they are targeting for recruitment. This trend is not reflective of national and regional trends for this age cohort." (p. 1). See: http://www.healthcoalition.ca/wp-content/uploads/2017/11/ATI-Request-CPR-in-SK-Response-Package-with-Redactions-2017-09-12.pdf (Accessed: Dec. 15, 2017).

7.2 Finally, we note that well-informed opponents of the compensatory model should not suggest that PDMPs, including Ig, made with compensated donors are riskier or less safe than PDMPs, including Ig, made with uncompensated donors. This presumption may be harmful to patients.